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PHYSICOCHEMICAL AND MECHANICAL CHARACTERIZATION OF HOT-MELT EXTRUDED DOSAGE FORMS

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PHYSICOCHEMICAL AND MECHANICAL CHARACTERIZATION OF HOT-MELT EXTRUDED DOSAGE FORMS

by

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DEDICATION

To Carrie:

For your unconditional love, patience and support.

To Mom and Dad:

For giving me the thirst for answers and the tools to find them.

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PHYSICOCHEMICAL AND MECHANICAL CHARACTERIZATION OF HOT-MELT EXTRUDED DOSAGE FORMS

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The physicochemical and mechanical properties and the mechanisms of drug release from drug delivery systems prepared by hot-melt extrusion were investigated. The influence of processing conditions and the thermal properties of the polymeric retardants was also studied.

The stability of polyethylene oxide (PEO) in sustained release tablets prepared by hot-melt extrusion was investigated. The chemical stability of PEO was found to be dependent on the storage and processing temperature, the screw speed and the molecular weight of the polymer. Lower molecular weight PEO MW = 100,000 (PEO 100K) was demonstrated to be a suitable processing aid for PEO 1M. Vitamin E, Vitamin E Succinate and Vitamin E TPGS were found to be suitable stabilizers for PEO; however, ascorbic acid was shown to degrade the polymer in solution. Drug release rates from hot-melt extruded tablets

stabilized with antioxidants were found to be dependent on the hydrophilic nature of the antioxidant. The physicochemical properties and mechanism of drug release from ethyl cellulose matrix tablets containing a water soluble drug (guaifenesin) were investigated. Tablets were prepared by direct compression and hot-melt extrusion techniques. The drug dissolution and release kinetics were determined and the tablet pore characteristics, tortuosity, thermal properties and surface morphologies were studied. The tortuosity was measured directly by a novel technique that allows for the calculation of diffusion coefficients in 3 experiments. The Higuchi diffusion model, percolation theory and polymer free volume theory were applied to the dissolution data to explain the release properties of drug from the matrix systems. Films containing PEO and two model drugs (guaifenesin and ketoprofen) were prepared by hot-melt extrusion. Both guaifenesin and ketoprofen were stable during the extrusion process. Wide angle X-ray diffraction suggested that guaifenesin crystallized from the melt upon cooling, but ketoprofen formed a solid solution. Crystallization of guaifenesin on the surface of the film could be observed using scanning electron microscopy at all concentrations studies, but did not reveal ketoprofen crystallization until reaching the 15% level. Guaifenesin and ketoprofen were found to

decrease the drive load, increase the stability of polyethylene oxide and plasticize the polymer during extrusion. The percent elongation decreased with increasing guaifenesin concentrations, but increased with increasing ketoprofen concentrations. Both guaifenesin and ketoprofen decreased the tensile strength of the film.

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CHAPTER 1 INTRODUCTION

1.1 PHARMACEUTICAL APPLICATIONS OF HOT-MELT EXTRUSION

Hot-melt extrusion is a widely applied processing technique within the plastics industry. Hot-melt extrusion is the process of pumping raw materials with a rotating screw under elevated temperature through a die into a product of uniform shape. Currently, more than half of all plastic products, including plastic bags, sheets, and pipes, are manufactured by this process [1]. Hot melt extrusion was first introduced in the plastics industry in the mid-nineteenth century to prepare polymeric insulation coatings to wires. Today, interest in hot-melt extrusion techniques for pharmaceutical applications is growing rapidly with over 100 papers published in the literature. The number of hot-melt extrusion patents issued for pharmaceutical systems has steadily increased since the early 1980's (Figure 1.1) with international scope (Figure 1.2).

Several research groups have demonstrated hot-melt extrusion processes as a viable method to prepare pharmaceutical drug delivery systems, including granules [2], pellets [3, 4], sustained release tablets [5-9], transdermal and transmucosal drug delivery systems [10-17] and

implants [18-21]. The hot-melt extrusion technique is an attractive alternative to traditional solvent casting methods.

Hot-melt extrusion offers many advantages over traditional pharmaceutical processing techniques. Molten polymers during the extrusion process can function as thermal binders and act as drug depots and/or drug release retardants upon cooling and solidification. Solvents and water are not necessary reducing the number of processing steps and eliminating time-consuming drying steps. The active ingredients do not need to be compressible and the entire procedure is continuous and efficient. The intense mixing and agitation imposed by the rotating screw cause de-aggregation of suspended particles in the molten polymer resulting in a more uniform dispersion. Hot-melt extrusion has been used to improve the bioavailability of drug substances by formation of molecular dispersions. Hot-melt extrusion requires a pharmaceutical grade polymer that can be processed at relatively low temperatures due to the thermal sensitivity of many drugs. All components must be thermally stable at the processing temperature during the short duration of the heating process.

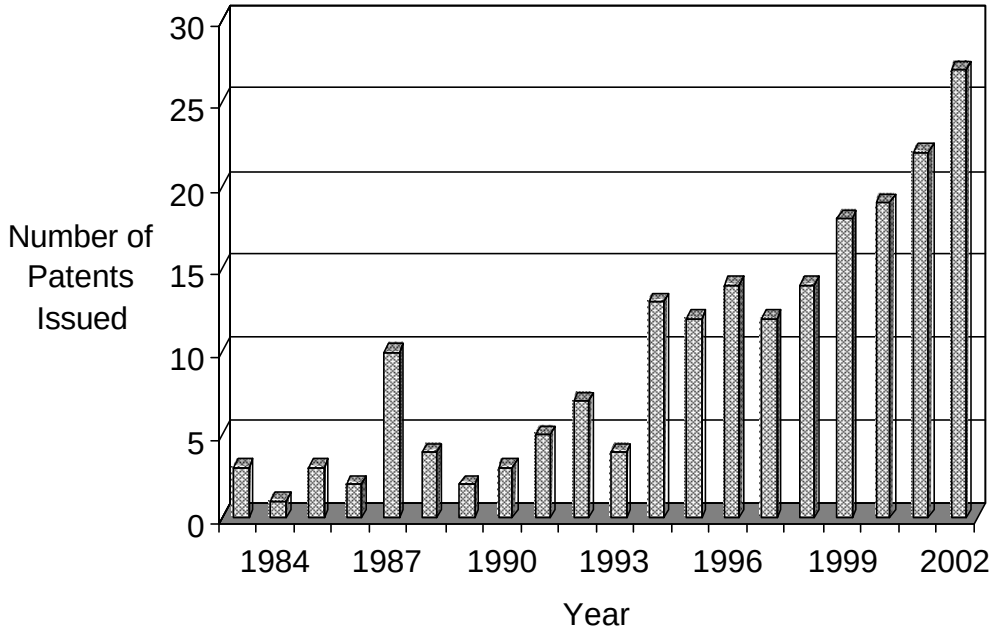

Figure 1.1: The number of hot-melt extrusion patents issued for pharmaceutical applications from 1983 to 2002.

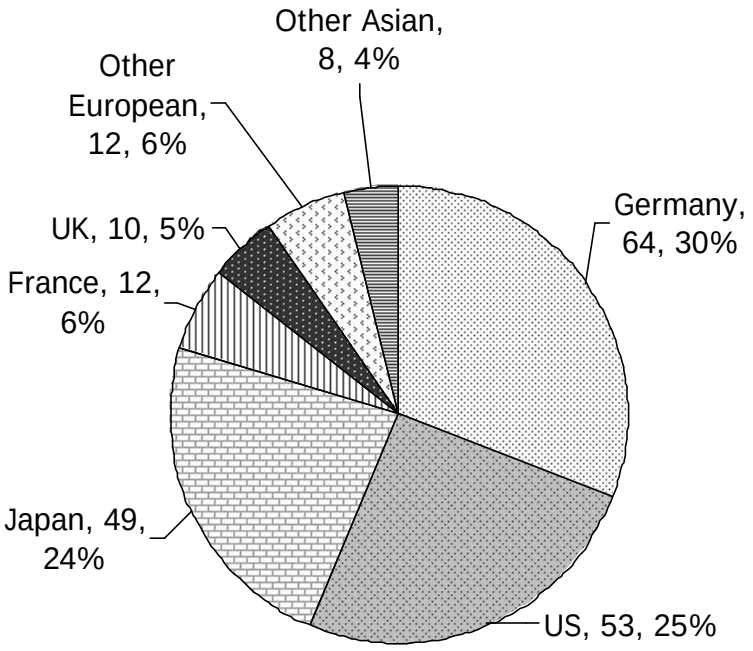

Figure 1.2: The number and percentage of hot-melt extrusion patents issued since 1983 for pharmaceutical applications by country.

1.2 EQUIPMENT, PRINCIPLES OF EXTRUSION AND PROCESS TECHNOLOGY

1.2.1 Hot-Melt Extrusion Equipment

Extrusion processes can be categorized as ram extrusion or screw extrusion. Screw extrusion consists of a rotating screw inside a heated barrel, while ram extrusion operates with a positive displacement ram capable of generating high pressures to push materials through the die. Materials are subjected to higher shear stress and more intense mixing in a screw extruder. Extrudates prepared by screw extrusion are more homogeneous, in comparison with extrudates that are processed by ram extrusion. Screw extruders include single screw and twin screw extruders. In a twin screw extruder, two screws can either rotate in the same (co-rotating extruder) or the opposite (counter-rotating extruder) direction. The first twin screw extruders were developed in the late 1930's in Italy. Twin screw extruders have several advantages over single screw extruders, such as easier material feeding, high kneading and dispersing capacities, less tendency to over heat and shorter transit time.

During ram extrusion, materials are introduced into a heated cylinder. After an induction period to soften the materials, a ram (or a

piston) pressurizes the soft materials through the die and transforms them into the desired shape. High-pressure is the operating principle of the ram extrusion. The major drawback of ram extrusion is limited melting capacity which causes poor temperature uniformity in the extrudate.

An extruder consists of three distinct parts: a conveying system for material transport and mixing, a die system for forming and downstream auxiliary equipment for cooling, cutting or collecting the finished goods. Individual components within the extruder are the feed hopper, barrel, screw, die, screw driving motor and heating and cooling systems (Figure 1.3). Standard process control and monitoring devices include temperature and screw speed with optional monitoring of torque, drive amperage, pressure and melt viscosity. Temperatures are normally controlled by electrical heating bands, and the temperature is monitored by thermocouples.

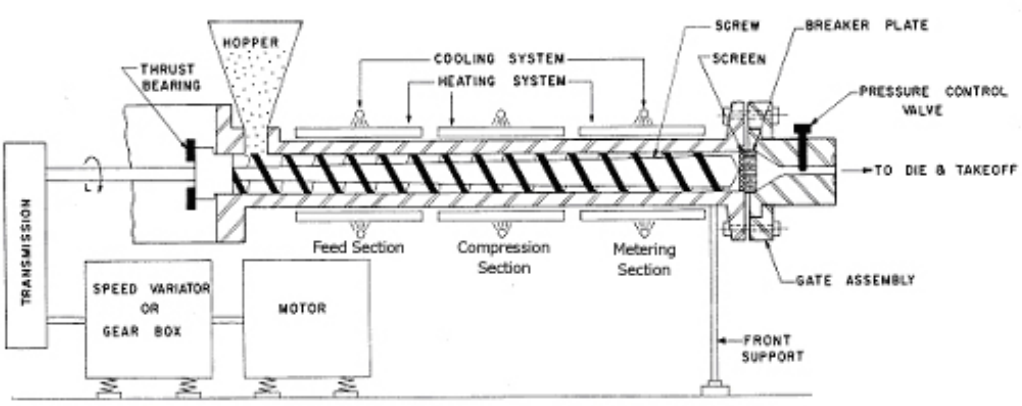

Figure 1.3: Schematic diagram of a single screw extruder.

(From Reference [22])

Most commercial extruders have a modular design to facilitate changing screws. The design of the screw has a significant impact on the process and can be selected to meet particular requirements such as high or low shear. Whelan and Dunning have reviewed the various screw designs available [23]. Specific screw features are displayed in Figure 1.4. Screws are designed with several sections, with the function of each section ranging from feeding, mixing, compression, and metering. Most screws are made from surface coated stainless steel to reduce friction and the possibility of chemical reactions.

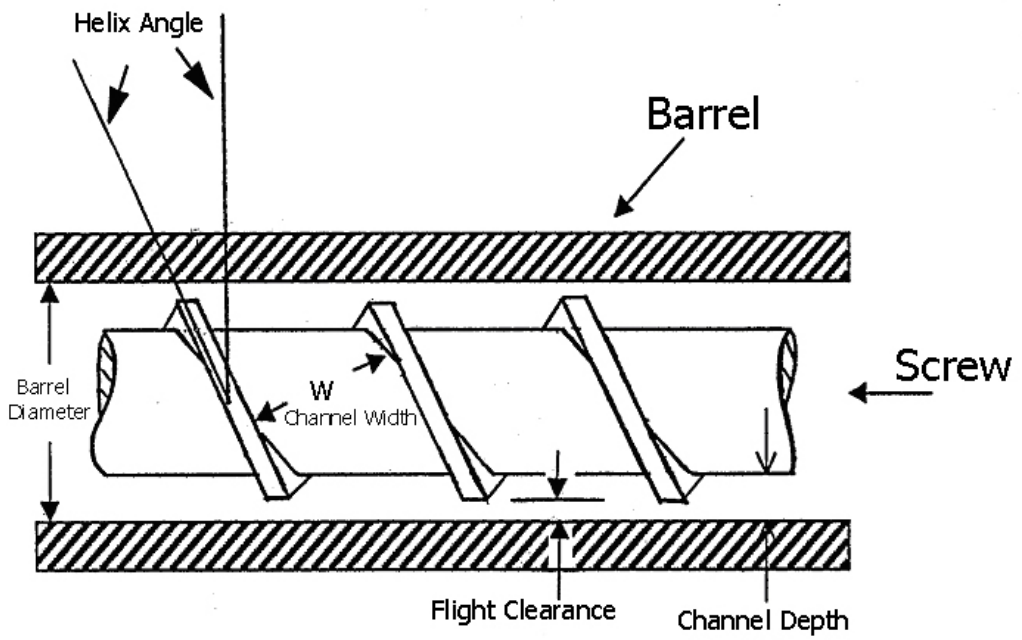

Figure 1.4: Diagram of an extruder screw.

The channel depth is the distance from the screw roots to the inner barrel surface, the flight clearance is the distance between the screw flight and the inner barrel surface, the channel width is the distance between two neighboring flights, the helix angle is the angle between the flight and the direction perpendicular to the screw axis.

The screw is typically divided into three sections along the length of the barrel: feeding, melting or compression, and metering as shown in Figure 1.3. The purpose of the feeding section is to transfer the materials from the hopper to the barrel. The channel depth is usually widest in this section to facilitate mass flow. A decrease in channel depth in the compression zone increases the pressure which removes entrapped air. The polymer typically begins to soften and melt in the compression zone. Thermoplastic polymers primarily exist in a molten state when entering the metering section. The mass flow rate of the extrudate is highly dependent upon the channel depth and the length of the metering section.

The die is attached at the end of the barrel. The shape of the die controls the form of the extrudate (Figure 1.5). Generally, the cross section of the extrudate will increase upon leaving the die, a phenomenon known as “die swell” due to the viscoelastic properties of polymers. This entropy driven event occurs as the individual polymer chains recover from the deformation imposed by the rotating screw by “relaxing” and increasing their radius of gyration.

Several types of downstream equipment are necessary to further process the extrudate into its desired form. Pelletizers are used to chop

small diameter rods into pellets or granules (Figure 1.6). For film applications, chill rolls and torque winders are used to rapidly cool and collect the extrudate (Figure 1.7). Film thickness can be adjusted by changing the rotation speed of the chill rolls or the torque winder.

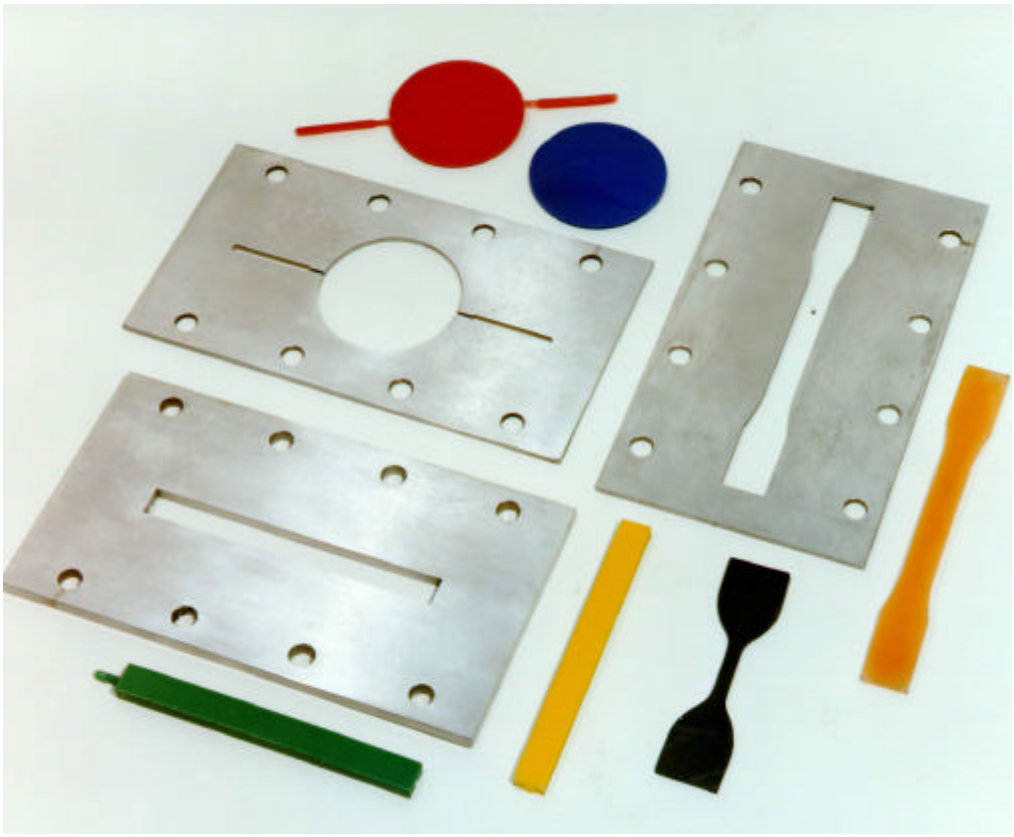

Figure 1.5: Illustration of dies and resultant extrudate shapes.

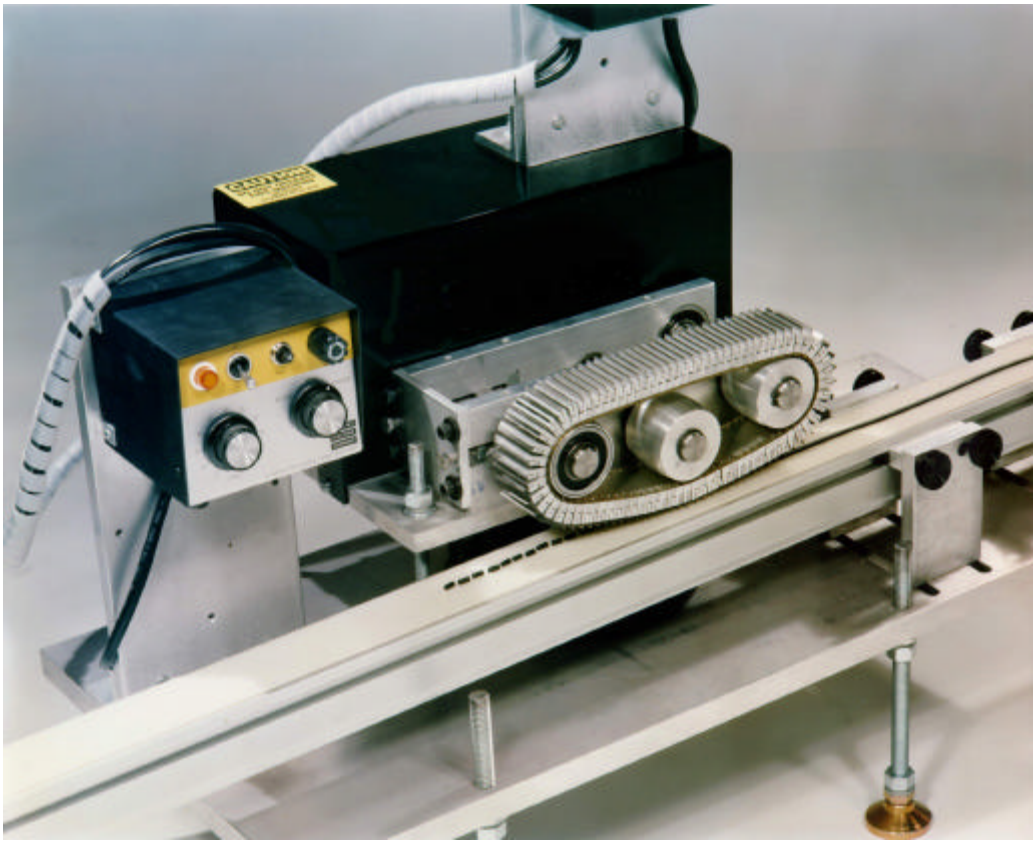

Figure 1.6: Illustration of a pelletizer used to chop rod shaped extrudates into pellets or granules.

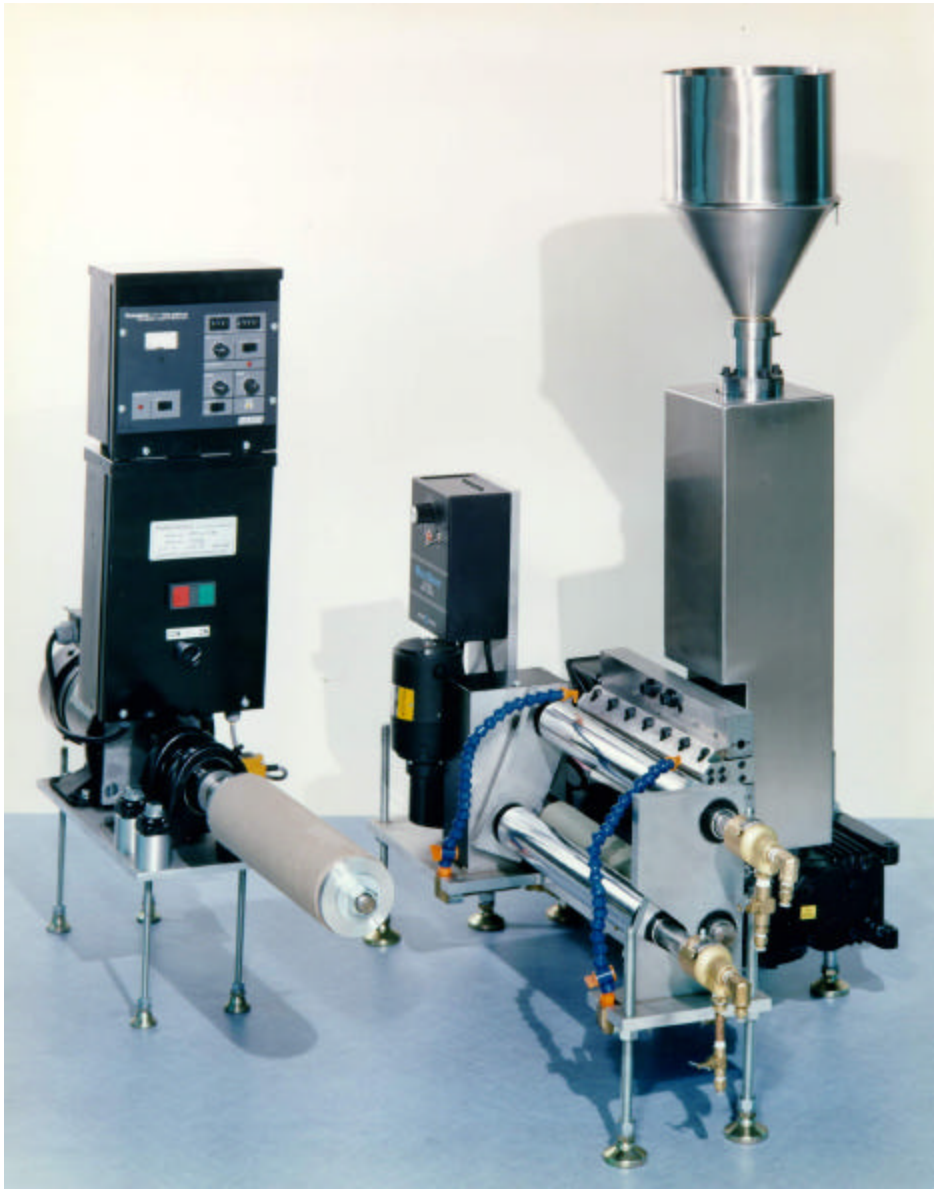

Figure 1.7: Illustration of a hot-melt extrusion film assembly with chill rolls and torque winder.

1.2.2 The Hot-Melt Extrusion Process

The different zones of the barrel are pre-set to specific temperatures before the extrusion process. The feed stock is placed in the hopper and transferred into the heated barrel by the rotating screw. The feed stock must have good flow properties. This requirement is usually met by insuring that the angle of the feed hopper exceeds the angle of repose of the feed materials. When this prerequisite is not met, the feed stock tends to form a solid bridge at the throat of the hopper resulting in erratic flow. In these situations, a force feeding device can be used.

As the feed stock is moved along the length of the barrel, heat is generated by shearing imposed by the rotating screw in addition to conduction from the electrical heating bands. The efficiency of the feeding section is dependent upon the friction coefficient between the feed materials and the surface of the barrel and screw. High friction along the barrel and low friction at the screw interface contribute to efficient mass flow in the feed section. Obviously, the bulk density, particle shape, and compression properties of the raw materials impact the feeding efficiency.

The transfer of the material should be efficient in order to maintain an increase in pressure in the compression zone and the metering zone. The pressure rise in these zones insures efficient output of the extrudate. It is also possible to fine-tune the barrel temperature at the feeding section in order to optimize the friction at the surface of the barrel. Inconsistent material feed may result in a "surge" phenomenon that will cause cyclical variations in the output rate, head pressure and product quality. The temperature of the melting zone is normally set 15 - 60°C above the melting point of semi-crystalline polymers or the glass transition temperature of amorphous polymers [22, 24-26].

The efficiency of the melting process depends on the polymer properties and the extruder design. In general, polymers with low melt viscosities and high thermal conductivities exhibit a more efficient melting process. Changes in the screw design are sometimes warranted to improve the melting process and improve mass flow through the extruder. Solidified polymer components can block the channel if melting is incomplete and result in a surge of material around the blockage.

Processing conditions depend on the chemical stability and physical properties of the thermal polymer. Melt viscosity, molecular weight, glass transition temperature, and melting point (in the case of a semicrystalline

polymer) should be considered to establish appropriate processing parameters. Polymers are subjected to a mechanical shear stress imposed by the rotating screw, and thermal stress due to the relatively high processing temperatures and pressures. Under these conditions, polymers may undergo chain scission, depolymerization or thermal degradation. Differential scanning calorimetry, thermogravimetric analysis and gel permeation chromatography are often used to monitor polymer stability. Plasticizers, antioxidants, thermal lubricants and other additives are often included in the formulation to address stability concerns.

1.2.3 Wet Extrusion versus Dry Extrusion

Based on the properties of the feed stock, extrusion processes can be classified as wet extrusion or dry extrusion. In wet extrusion, the feed stock is conditioned and softened with the addition of solvents prior to processing. The primary reason for wet extrusion is that extrudates have a superior finish due to the softening, plasticizing and ripening action of the solvents. In some cases, such as cellulose nitrate, wet extrusion under low temperatures and pressures with minimum friction is required because the polymer is explosive when overheated using dry extrusion processes.

Compared with wet extrusion, dry extrusion is a solvent free process. The feed stock is generally in solid form and heat is required to soften or melt the materials. In the dry extrusion process, materials are softened by the heated barrel, the shearing effect of a rotating screw and friction during transit. The extrudate solidifies after exiting the extruder. For obvious reasons, most of the extrusion processes use the dry technique.

1.2.4 Mass Flow during Hot-Melt Extrusion

Polymer melts behave as pseudoplastic fluids under typical processing conditions. The viscosity of a pseudoplastic fluid depends upon the shear rate and is described by the following power law equation (Equation 1.1):

$$h = K \times g^{n-1} \qquad \text{(Equation 1.1)}$$

where h is the viscosity of the polymer melt, g is the shear rate, K is an exponential function of the temperature and depends on the properties of the polymer, and n is the power law constant (typically in the range of 0.25 to 0.9 for the polymer melt).

Minimum temperatures are required for extrusion; otherwise, the torque required to rotate the screw will overload the drive unit. Torque is directly proportional to melt viscosity. The dependence of polymer melt viscosity on the temperature at a given shear rate follows the Arrhenius equation (Equation 1.2):

$$h = K' \times e^{Ea/RT} \qquad \text{(Equation 1.2)}$$

In equation 1.2, *K'* is a constant depending on the structure and the molecular weight of the polymer; *Ea* is the activation energy of the polymer for the flow process, and it is a constant for the same type of polymer; *R* is the gas constant; and *T* is the temperature in degrees Kelvin.

Heat conduction from the electrical bands on the barrel contributes to the melting process. However, heat is also generated from shearing of the polymer melt. "Viscous heat generation" is the process of transforming mechanical energy from shearing into thermal energy. The rate of heat generation per unit volume due to the viscous heat dissipation follows Equation 1.3:

$$E = m \times g^{n+1} \qquad \text{(Equation 1.3)}$$

in which m is a constant, g is the shear rate and n is the power law constant [24].

1.3 MATERIALS USED IN HOT-MELT EXTRUSION

For a pharmaceutical material to be processed by hot-melt extrusion, it must be able to deform easily inside the extruder and solidify upon its exit. The materials must meet the same levels of purity and safety as those prepared by traditional techniques. Most of the raw materials used in hot-melt extruded pharmaceuticals have been used in the production of other solid dosage forms such as tablets, pellets, granules and transdermals. Thermal stability of the individual compounds is a prerequisite for the process, although the short processing times encountered in this process may not limit all thermolabile compounds.

Hot-melt extruded dosage forms are complex mixtures of active medicaments and functional excipients. Functional excipients may be broadly classified as matrix carriers, release modifying agents, bulking agents, antioxidants, thermal lubricants and miscellaneous additives. The

selection and use of various excipients can impart specific properties to hot-melt extruded pharmaceuticals in a manner similar to those in traditional dosage forms.

The incorporation of plasticizers may lower the processing temperatures necessary for hot-melt extrusion thus reducing drug and carrier degradation. Drug release from these systems can be modulated by the incorporation of various functional excipients. The dissolution rate of the active compound can be increased or decreased depending on the properties of the rate-modifying agent. For systems that display oxidative or free radical degradation during processing or storage, the addition of antioxidants, acid acceptors, and/or light absorbers may be warranted.

1.3.1 Carriers

In hot-melt extruded drug delivery systems, the active compound is embedded in a carrier formulation comprised of one or more “meltable” substances and other functional excipients. The meltable substance is generally a polymer or low melting point wax. The selection of an appropriate carrier is important in the formulation and design of a hot-melt extruded dosage form. The properties of the carrier often dictate the processing conditions. The physical and chemical properties of the carrier

can control the release of the active compound from the final dosage form. Table 1.1 lists some of the carriers used to prepare hot-melt extruded dosage forms.

For systems employing non-polymeric carrier materials, the compatibility between the drug substance and carrier should be addressed. The incorporation of a low melting compound into a low melting point wax may form a eutectic mixture or reduce the melting point of the mixture preventing the formation of a solid dosage form. The production of granules using carnauba wax has been reported [27-29]. The granules contained diclofenac sodium and could be produced at temperatures less than the reported melting point of the wax material. The use of waxes and other wax-based materials have the potential advantage of being relatively inert.

Table 1.1 Carriers used to prepare hot-melt extruded dosage forms

Chemical Name	Trade Name	Tg (°C)	Tm (°C)	References
Ammonio methacrylate copolymer	Eudragit® RS/RL	64	--	[3, 30, 31]
Poly(dimethylaminoethylmethacrylate-co-methacrylic esters)	Eudragit® E	50	--	[10, 14, 16]
Poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid) 7:3:1	Eudragit® 4135F	48	--	[4]
Poly(methacrylic acid-co-methyl methacrylate) 1:2	Eudragit® S	160	--	[2]
Hydroxypropyl cellulose	Klucel®	130	--	[11-16, 29]
Ethyl cellulose	Ethocel®	133	--	[2, 3, 8, 32]
Cellulose acetate butyrate	CAB 381-0.5	125	157	[2, 3, 33]
Cellulose Acetate Phthalate	--	165	192	[2, 34]
Poly(ethylene oxide)	Polyox® WSR	-50	65-80	[5, 7, 9, 11-13]
Poly(ethylene glycol)	Carbowax®	-20	37-63	[16, 35-39] [40]
Poly(vinyl pyrrolidone)	Kollidon®	168	--	[2, 38, 39, 41-43]
Poly(vinyl acetate)	Sentry® plus	35-40	--	[6, 33]
Hydroxypropyl Methylcellulose Phthalate	--	137	150	[2, 44]
Polyvinylpyrrolidone-co-vinyl acetate	Kollidon® VA64	--	--	[36, 38, 45]

Table 1.1 (continued)

Hydroxypropyl Methylcellulose	Methocel®	175	--	[46]
Hydroxypropyl Methylcellulose Acetate Succinate	Aqoat-AS®	--	--	[47]
Poly(lactide-co-glycolide)	PLGA	--	--	[19, 20]
Polyvinyl Alcohol	Elvanol®	--	--	[2]
Chitosan Lactate	Sea-Cure®	--	--	[2]
Pectin	Obipektin®	--	--	[2]
Carbomer	Carbopol® 974P	--	--	[14, 16]
Polycarbophil	Noveon® AA-1	--	--	[14, 16]
Poly(ethylene-co-vinyl acetate)	Elvax® 40W	-36	45	[3, 48, 49]
Polyethylene	--	-125	140	[10] [33]
Poly(vinyl acetate-co-methacrylic acid)	CIBA-I	--	84-145	[50]
Epoxy resin containing secondary amine	CIBA HI	80-100	--	[50]
Polycaprolactone	--	--	--	[33]
Carnauba Wax	--	--	82-85	[27-29]
Ethylene-vinyl acetate copolymer	Evatane®	--	--	[51]

Table 1.1 (continued)

Glyceryl Palmitostearate	Precirol® ATO 5	--	52 – 55	[46]
Hydrogenated Castor & Soybean Oil	Sterotex® K	--	--	[46]
Microcrystalline Wax	Lunacera® Paracera®	--	--	[52, 53]
Corn Starch	--	--	--	[54-56]
Maltodextrin	--	--	--	[53]
Pregelatinized Starch	--	--	--	[53]
Isomalt	Palatinit®	--	145-150	[57-59]
Potato Starch	--	--	--	[60, 61]
Citric Acid	--	--	153	[62-64]
Sodium Bicarbonate	--	--	--	[62-64]

Drug release kinetics from hot-melt extruded dosage forms are highly dependent upon the choice of the carrier material. Carriers used in hot-melt extruded dosage forms have included water insoluble polymers and waxes such as ethyl cellulose or carnauba wax in which the rate of drug release is diffusion controlled. Water soluble polymers have included hydroxypropyl cellulose, polyethylene oxide, poly(vinyl pyrrolidone) in which the drug is released by a diffusion and erosion mechanism. Functional excipients have also been used to modify drug release rates in these systems. Depending upon the physical and chemical properties of these additional excipients, various release profiles may be achieved. Functional excipients have been formulated into hot-melt extruded dosage forms to modify the drug release rate by altering the porosity or tortuosity of the dosage form. Viscosity increasing agents have been incorporated into polymeric matrices to limit and reduce the initial burst often observed with these systems.

The use of ionic and / or pH dependent polymers as the carrier matrix may achieve zero-order drug release or site specific drug delivery along the gastrointestinal tract. Swelling agents and super disintegrants such as AcDiSol® and Explotab® have been investigated as a method to

modulate drug release. It has been reported that Explotab® could be used as a "super-absorbent" in hydroxypropylcellulose hot-melt extruded transdermal films to facilitate moisture uptake in wound care applications [14]. A similar approach of drug release modification was applied to wax-containing systems [27-29]. Hydroxypropylcellulose, Eudragit® L, and sodium chloride were incorporated into diclofenac sodium/carnauba wax matrices. Increasing the cellulose derivative or methacrylic acid copolymer concentration in the system resulted in a substantial increase in the release of diclofenac sodium. The release of diclofenac sodium from hydroxypropylcellulose/wax matrices was less pH dependent than the system containing wax/Eudragit® L since the methacrylic acid copolymer is insoluble in water or in solutions with pH<6. The effect of sodium chloride was less pronounced and was attributed to the negligible swelling effect of this material.

1.3.2 Plasticizers

Plasticizers are typically low molecular weight compounds capable of softening polymers to make them more flexible. The use of polymeric carriers in hot-melt extrusion often requires the incorporation of a plasticizer into the formulation to improve the processing conditions

during the manufacturing of the extruded dosage form or to improve the physical and mechanical properties of the final product.

Plasticization of the polymer is generally attributed to the inter-molecular secondary valence forces between the plasticizer and the polymer. Plasticizers are able to decrease the glass transition temperature and the melt viscosity of a polymer by increasing the free volume between polymer chains. In so doing, the ease of movement of polymer chains with respect to each other is dramatically reduced. Plasticizers were also found to facilitate the fusion process of semi-crystalline polymers [65, 66]. Less energy is usually required to melt semi-crystalline polymers following the addition of one or more plasticizers. With the addition of a plasticizer, a hot-melt extrusion process can be conducted at lower temperatures and with less torque. Both the active ingredient and the polymer will be more stable during the extrusion process due to these improved processing conditions. Materials that are commonly used as plasticizers which are approved by the Food and Drug Administration for use in pharmaceutical dosage forms are listed in Table 1.2 according to their chemical structure.

Plasticizers used for the preparation of pharmaceutical dosage forms must have good efficiency, stability, polymer – plasticizer compatibility and permanence. Triacetin [3], citrate esters [10, 12], and

low molecular weight polyethylene glycols [3, 5, 12] have been investigated as plasticizers in hot-melt extruded systems. Additionally, several drug substances have been reported to function as plasticizers in hot-melt extruded dosage forms [5, 7, 8, 10, 12].

The physical and mechanical properties and drug release rate of pharmaceutical dosage forms is dependent on the permanence of the plasticizers. Permanence of a plasticizer during processing and storage is very important and the evaporation of highly volatile plasticizers from the dosage form during storage has been reported. Arwidsson and coworkers [67] reported a dramatic change in drug release properties of coated tablets due to volatilization of the plasticizer during curing and storage. Repka and McGinity [12] demonstrated that the amount of plasticizer remaining in hot-melt extruded films over time was a function of the plasticizer type and storage conditions. Plasticizers may also improve the physical-mechanical properties of hot-melt extruded dosage forms. In transdermal films, the addition of a plasticizer to the polymer matrix can improve the film's flexibility [10, 12]. Plasticizers often influence the product's tensile strength and elastic modulus.

Table 1.2 Common plasticizers used in pharmaceutical dosage forms

Type	Examples
Citrate esters	triethyl citrate, tributyl citrate, acetyl triethyl citrate, acetyl tributyl citrate
Fatty acid esters	butyl stearate, glycerol monostearate, stearyl alcohol
Sebacate esters	dibutyl sebacate
Phthalate esters	diethyl phthalate, dibutyl phthalate, dioctyl phosphate
Glycol derivatives	Polyethylene glycol, propylene glycol
Others	triacetin, mineral oil, castor oil

1.3.3 Other Processing Aids

The excessive temperatures needed to process unplasticized or under plasticized polymers may lead to polymer degradation. The stability of polymers that are susceptible to degradation can be improved with the addition of antioxidants, acid receptors and or light absorbers during hot-melt extrusion. One manufacturer of these materials recommends the incorporation of an antioxidant into formulations containing low molecular weight hydroxypropylcellulose [68]. Similarly, polyethylene oxide has been reported to be protected from free radical and oxidative degradation by the incorporation of an antioxidant [7].

Antioxidants are classified as preventive antioxidants or chain-breaking antioxidants based upon their mechanism. Preventive antioxidants include materials that act to prevent initiation of free radical chain reactions. Reducing agents, such as ascorbic acid, are able to interfere with autoxidation in a preventive manner since they preferentially undergo oxidation. The preferential oxidation of reducing agents protects drugs, polymers and other excipients from attack by oxygen molecules. These antioxidants are sometimes called oxygen scavengers. They are most effective when used in a closed system where

oxygen can not be replaced once it is consumed. Chelating agents such as edetate disodium (EDTA) and citric acid are another type of preventive antioxidant that decrease the rate of free radical formation by forming a stable complex with metal ions that catalyze these reduction reactions.

Hindered phenols and aromatic amines are the two major groups of chain breaking antioxidants that inhibit free radical chain reactions. Commonly used antioxidants such as butylated hydroxyanisole, butylated hydroxytoluene and vitamin E are hindered phenols. Because the O-H bonds of phenols and the N-H bonds of aromatic amines are very weak, the rate of oxidation is generally higher with the antioxidant than with the polymer.

Other materials have been used to facilitate hot-melt extrusion processing. Waxy materials like glyceryl monostearate have been reported to function as a thermal lubricant during hot-melt processing. Vitamin E TPGS has been reported to plasticize polymers and enhance drug absorption (Table 1.3).

Table 1.3 Common processing aids used in hot-melt extruded dosage forms

Chemical Name	Trade Name	Refererence(s)
Saccharose monopalmitate	Sucroester	[36, 43]
Glycerolester and PEG esters	Gelucire 44/14	[36]
Glyceryl monostearate	Imwitor	[54-56]
d-α-tocopherol (Vitamin E)	--	[7]
Vitamin E Succinate	--	[7]
Vitamin E TPGS	--	[7, 13, 16]
Butylated Hydroxy Anisole	--	[7]

1.3.4 Drugs

The properties of the active drug substance often limit the formulation and processing choices available to the pharmaceutical scientist in the development of dosage forms. Hot-melt extrusion offers many benefits over traditional processing techniques. The process is anhydrous which avoids potential hydrolytic degradation pathways. In addition, poorly compactable materials can be prepared as tablets without the compression process. Hot-melt extruded tablets can be produced by cutting an extruded rod to the desired dimensions.

As an initial assessment, the thermal, chemical, and physical properties of the drug substance must be characterized. Depending on the unique properties of the drug substance and the other materials in the formulation, the drug may be present as undissolved particles, a solid solution, or a combination in the final dosage form. The state of the drug in the dosage form may have a profound impact on the processability and stability of the product. The advantages and disadvantages of each form have been discussed in both injection molding [37] and melt extrusion [69] systems. Solid dispersion systems may be more stable and more easily processed than solid solution systems, but solid solution systems

may be produced that are transparent and may have increased bioavailability of poorly soluble compounds. Table 1.4 gives a partial listing of some of the drug substances that have been formulated and processed by hot-melt extrusion.

The active compound may help or hinder the functionality of the other components in the formulation. Oxprenolol hydrochloride was shown to melt under the hot-melt extrusion processing conditions thus decreasing the viscosity of the extrudate to yield a material with poor handling properties [3]. In similar work preparing dosage forms by injection molding, Cuff and Raouf reported that fenoprofen calcium inhibited the hardening of a PEG-MCC matrix, resulting in an unusable product [37]. In contrast, Lidocaine was shown to lower the glass transition temperature of Eudragit® E/HDPE films [10], and hydrocortisone demonstrated a time dependent lowering of the glass transition temperature of HPC films [12]. Thus, the drug substance can be both beneficial or detrimental to properties of hot-melt extruded dosage forms.

Table 1.4 Drug Substances processed by hot-melt extrusion techniques.

Drug	Tm (°C)	Reference(s)
Nifedipine	175	[42, 44, 45]
Indomethacin	162.7	[38, 42, 45]
Piroxicam	204.9	[42]
Tolbutamide	128.4	[42, 45]
Lacidipine	184.8	[38, 42, 45]
Chlorpheniramine Maleate	135	[5, 7, 12, 15, 30]
Theophylline	255	[4, 6, 33, 54-56]
17β-estradiol hemihydrate	--	[36, 43]
Oxprenolol hydrochloride	--	[3]
Fenoprofen calcium	--	[37]
Lidocaine	--	[10]
Hydrocortisone	--	[12]
Phenylpropanolamine Hydrochloride	192	[46]
Hydrochlorothiazide	274	[41, 58, 59]
Carbamazepine	192	[35]

Table 1.4 (continued)

Drug	Tm (°C)	Reference(s)
Ibuprofen	76	[31, 32, 53]
Melanotan-1		[19, 20]
Diclofenac Sodium	284	[29]
TAS 301		[70]
Acetaminophen	170	[57]
Nicardipine Hydrochloride	180	[47]
Etonogestrel	200	[48, 49]
Ethinyl estradiol	144	[48]
Acetylsalicylic Acid	135	[60, 61]
Diltiazem Hydrochloride	210	[3]

1.4 PROPERTIES OF HOT-MELT EXTRUDED DOSAGE FORMS

1.4.1 Chemical Stability of Drug Substances during Hot-Melt Extrusion

The stability of the active ingredients during hot-melt extrusion should be closely monitored since it is conducted at elevated temperatures. Hydrolysis, solvolysis and oxidation are three primary mechanisms of drug degradation. Drugs containing carboxylic acids, phosphoric acids or carbonyl functional groups are vulnerable to hydrolysis [71]. Water or a solvent must be present for hydrolysis or solvolysis to occur. Since hot-melt extrusion is a solvent free process, hydrolysis and solvolysis are often not a concern. Oxidation is also a free-radical chain reaction with three distinctive stages: initiation, propagation and termination. Oxidative drug degradation during hot-melt extrusion has been reported by Aitken-Nicol [10] and Repka [12]. Peroxides formed due to the oxidation of polymeric carrier were shown to induce the oxidation of the active ingredient [72]. Since the drug and polymer share the same oxidation mechanisms, antioxidants for polymers discussed in the previous chapter are also applicable for active ingredients.

High-pressure liquid chromatography is the most commonly used technique to investigate the stability of drug substances. Stability indicating methods should be developed so that the active ingredient is separated from the degradants. The purity of drug peak can be studied using a photo diode-array detector to confirm the reliability of the assay.

1.4.2 Thermal and Crystalline Properties of Hot-Melt Extruded Dosage Forms

Drug and polymers are subjected to elevated temperatures, high pressure and intense mixing during the hot-melt extrusion process. At these elevated temperatures, the solubility of the drug in the polymer carrier is increased. Depending upon the processing conditions, some crystalline drugs either melt or become solubilized in the polymer matrix during the process. Recrystallization and nucleation of drug molecules from the polymer melt is retarded during the cooling of the extrudate due to reduced solute migration and the difficulty in nucleation in a highly viscous polymer medium. Furthermore, polymer viscosity increases dramatically with the decrease in the temperature.

Following hot-melt extrusion, the active ingredient can be present in one of two forms: as a crystal embedded in the hardened polymer

phase, or as individual molecules dissolved in the polymer matrix. Formation of a drug-polymer solid dispersion in hot-melt extruded dosage forms has been reported [6, 10]. Complexation between drug and polymer may also contribute to the formation of a solid solution [73]. Solid solutions containing the drug and an amorphous polymer are generally regarded as interstitial solid solutions where drug molecules occupy the interstitial space between the polymer chains. For a semi-crystalline polymer, some drugs were reported to be concentrated in the amorphous regions of the polymer [74], and some drugs were reported to be solubilized in the crystalline matrix of the polymer [75]. Because the drug is dispersed at a molecular level, a solid dispersion is a metastable form. It is susceptible to aging effect and the drug may recrystallize from the matrix during the storage under elevated temperature and high humidity. Crystallization of chloramphenicol palmitate from the solid dispersion in PVP was reported [75].

The methods that have been used to characterize hot-melt extrudates are summarized in Table 1.5. In addition to characterizing the hot-melt extrudate, these methods can be used to differentiate between solid solutions (molecularly dispersed drug), solid dispersions in which drug is only partly molecularly dispersed and physical mixtures of drug

and carrier. It is challenging to precisely characterize systems which are molecularly dispersed from those that are not due to the complexity of the systems, and different analytical methods may yield contrasting results. In general, dispersions in which no crystallinity can be detected are molecularly dispersed and the absence of crystallinity is used as a criterion to differentiate between solid solutions and solid dispersions.

Thermoanalytical methods include those that examine the system as a function of temperature. Differential scanning calorimetry (DSC) has been widely used to study the thermal properties of materials used in hot-melt extrusion. DSC can be used for the quantitative detection of transitions (melting point, glass transition) in which energy is required or liberated (i.e. endothermic and exothermic phase transformations). Generally, the hot-melt extrudate is scanned and compared to a physical mixture of the drug, polymeric carrier and other excipients. The lack of a melting transition in the DSC scan of the hot-melt extrudate indicates that the drug is present in an amorphous rather than crystalline form. Thermogravimetric analysis (TGA) is a measure of thermally induced weight loss of a material as a function of applied temperature. TGA is limited to studies involving either a weight gain or loss, and is commonly used to study desolvation and decomposition. TGA can be used as a

screening tool for the thermal stability of materials used in hot-melt extrusion. Microthermal analysis has been used to identify phase separation in hot-melt extrudates containing itraconazole and Eudragit E100 [76]. In this approach, differences in the thermal topography of hot-melt extrudates can be discerned.

X-ray diffraction (XRD) is also used to characterize the crystalline properties of hot-melt extruded dosage forms. The principle of XRD is based on Bragg's law, in which parallel incident X-rays strike the crystal planes and are then diffracted at angles related to the spacing between the planes of molecules in the lattice. Crystallinity is reflected by a characteristic fingerprint region in the diffraction pattern. If the fingerprints of the drug and carrier do not overlay one another, the crystallinity of the drug and polymer following hot-melt extrusion can be determined. Thus, X-ray diffraction can be used to differentiate between solid solutions, in which the drug is amorphous, and solid dispersions, in which it is at least partly present in the crystalline form, regardless of whether the carrier is amorphous or crystalline. However, the sensitivity of the XRD technique is limited and cannot generally detect crystallinity of less than 10% [77].

Infrared spectroscopy can be used to detect changes in bonding between functional groups due to structural changes or a lack of crystal structure. IR can be used to differentiate between peaks that are sensitive to changes in crystallinity from those that are not [78]. Solid state nuclear magnetic resonance (NMR) has been used to probe the crystallinity of materials. Although any NMR-active nucleus can be studied, most efforts have focused on ^{13}C investigations.

Microscopy is one of the best methods to study the crystalline properties of hot-melt extrudates. Both optical and electron methods are suitable to examine the surface morphology of samples to probe for the presence of crystalline particles or amorphous domains. It is also possible to obtain reliable particle size information using these techniques.

Table 1.5: Common Methods used for the characterization of hot-melt extrudates.

Thermoanalytical Methods	Differential Scanning Calorimetry Thermogravimetric Analysis Hot Stage Microscopy Microthermal Analysis
Dissolution Testing	
X-Ray Diffraction	Wide Angle X-Ray Diffraction
Spectroscopic Methods	IR
Microscopic Methods	Polarized Light Microscopy Scanning Electron Microscopy Transmission Electron Microscopy Atomic Force Microscopy
Nuclear Magnetic Resonance	Magic Angle Spinning Techniques Cross-Polarization Techniques
Mechanical Analysis	Tensile Strength Elongation Young's Modulus

1.5 HOT-MELT EXTRUDED DOSAGE FORMS

1.5.1 Granules, Pellets & Spheres

Until recently, hot-melt extrusion had not received much attention in the pharmaceutical literature. Rippie and Johnson prepared pellets containing cellulose acetate phthalate using a rudimentary ram extruder in 1969 to study the dissolution rates based upon pellet geometry [34]. More recently, Mank and coworkers reported in 1989 and 1990 on the extrusion of a number of thermoplastic polymers to produce sustained release pellets [79, 80].

Follonier and coworkers in 1994 investigated the possibility of using hot-melt extrusion technology to produce sustained-release pellets [3]. It was the researchers' goal to prepare a dosage form in a simple and continuous manner. Thermal degradation was recognized as a limitation of this hot-melt process. Diltiazem hydrochloride, a relatively stable and freely soluble drug was incorporated into their polymer–based pellets for sustained release capsules. Polymers and plasticizers were selected prior to extrusion to maximize the possibility of a successful dosage form. In their study, ethyl cellulose, cellulose acetate butyrate, poly(ethyl acrylate/methyl-methacrylate/trimethyl ammonio ethyl methacrylate

chloride) (Eudragit® RSPM) and poly(ethylene-co-vinyl acetate) (EVAC) were the polymers and the plasticizers were triacetin and diethyl phthalate. The porosity of the pellets was determined by mercury porosimetry. The pellets exhibited a smooth surface and low porosity. The drug release characteristics of diltiazem were biphasic, with the CAB and EVAC pellets giving the slowest release rate. These researchers also reported that the type and amount of plasticizer used, drying time of the polymers, extrusion temperatures, and plasticization times varied with each formulation. They observed that the stability of Eudragit® RSPM was adequate for extrusion at a temperature of 130°C.

In a latter study, Follonier, et al. examined different parameters influencing the release of diltiazem hydrochloride from hot-melt extruded pellets incorporated into hard gelatin capsules [2]. The drug release rate was found to depend upon polymer type, addition of pore-forming additives or hydrophilic polymers, and pellet size. The authors obtained in vitro release rates low enough to achieve therapeutic plasma levels for diltiazem hydrochloride with a once or twice daily administration. The addition of hydrophilic polymers helped avoid incomplete drug release due to encapsulated drug clusters in the insoluble matrix. The authors also

incorporated various polymeric excipients, such as croscarmellose sodium (Ac-Di-Sol®) and sodium starch glycolate (Explotab®), into the pellet formulations to vary the drug release rate. The incorporation of swelling agents was able to reduce the initial burst release from the matrix.

In 1996 and 1997, Miyagawa, Sato, and coworkers prepared controlled release matrices containing diclofenac as a model drug by hot-melt extrusion [27-29]. The authors used a twin-screw compounding extruder to prepare wax matrix granules composed of carnauba wax, the model drug, and other rate controlling agents. Their study showed that a wax matrix with high mechanical strength could be obtained even when the composition was processed below the melting point of the wax. Dissolution of diclofenac from the wax matrix granules was strongly influenced by the formulation. Hydroxypropylcellulose, methacrylic acid copolymer (Eudragit L-100), and sodium chloride were investigated as dissolution rate controlling materials. The authors emphasized the advantages of using the twin-screw extruder for wax matrix tablets because of the low processing temperatures, high kneading and dispersing ability, and short residence time. The authors observed in their second study that the selection of rate controlling excipients based upon

solubility and swelling characteristics had a significant impact on drug release properties from the wax matrix granules.

Liu and coworkers [46] compared the properties of wax based granules and tablets prepared by hot-melt extrusion to those prepared by high shear melt granulation. Powder blends containing phenylpropanolamine hydrochloride, Precirol®, Sterotex® K, and various excipients (microcrystalline cellulose, lactose and Emcompress®) were extruded using a single screw extruder with open end discharge. The extrudates were then passed through a 14-mesh screen to form granules. Hot-melt extruded granules were observed to be less spherical than high-shear melt granules and had lower bulk and tap densities. Analysis of the hot-melt extruded granules showed better drug content uniformity among granules of different size ranges compared with high-shear melt granules, resulting in a more reproducible drug release from the corresponding tablets. At the same wax level, drug release from tablets decreased in the order of using microcrystalline cellulose, lactose and Emcompress® as the filler excipient. The observed differences in the dissolution properties of the tablets were due to the differences in the solubility, swellability and density of the filler excipients.

Hot-melt extrusion has also been used to prepare effervescent granules [62-64, 81-84]. Lindberg and coworkers prepared effervescent granules using a twin-screw extruder. During extrusion, sodium bicarbonate and anhydrous citric acid were added from separate inlet ports of the extruder, and ethanol was added as a liquid binder and pumped through a nozzle in the extruder barrel to facilitate the formation of the granules.

Koleng and McGinity utilized hot-melt extrusion technology for the preparation of rapid release granules [40]. A hot-melt extrusion process was used to granulate acetaminophen and filler excipients with low molecular weight poly(ethylene glycol)s. The resultant granules were then combined with additional excipients (disintegrants and lubricant) and compressed into tablet compacts. The granules exhibited improved drug release compared to the tablets. Tablets containing 15% poly(ethylene glycol) released greater than 80% of the incorporated acetaminophen after 30 minutes, as required for acetaminophen tablets in the USP 23.

Zhang investigated the properties of poly(vinyl acetate) as a carrier for theophylline from matrix dosage forms prepared by hot-melt extrusion [6]. The influence of granule size and drug loading level on the drug release properties and the thermal stability of poly(vinyl acetate) (PVAc)

were investigated. The rod shaped extrudates were ground and then compressed into tablets with various combinations of microcrystalline cellulose. As the size of the hot-melt extruded theophylline/PVAc granules was increased, a significant decrease in the release rate of the theophylline was observed. Since the drug was released from the matrix by a diffusion mechanism, the decrease in the drug release rate from the tablets containing larger granules was concluded to be a result of a longer diffusion pathway. PVAc was found to have a high solids carrying capacity when processed by hot-melt extrusion, with drugs loads as high as 50%. The authors also studied the stability of PVAc to shear and stress using a Plasticorder® rheometer. The torque gradually decreased as the temperature of the polymer melt in the chamber was increased. No further change in the torque was observed after the initial heating step. This finding confirmed that PVAc was not susceptible to degradation by either thermal or shearing stress under the processing conditions.

Hot-melt extrusion has been used to prepare solid dispersions for immediate and sustained release applications. It has also been used to prepare solid dispersions in which the drug dissolution rate is enhanced. Huslman and coworkers demonstrated the hot-melt extrusion technique to increase the solubility rate of 17-Estradiol hemihydrate, a poorly water-

soluble drug [36, 43, 85]. The authors used PEG 6000, PVP or a vinylpyrrolidone – vinylacetate copolymer as polymers with Sucroester WE15 or Gelucire 44/14 as functional excipients. Rods were extruded, cut into granules and then compressed into tablets. The solid dispersions exhibited a significant increase in dissolution rate compared to the pure drug or to the physical mixtures. A 30-fold increase in dissolution rate was obtained from a formulation containing 10% 17-Estradiol, 50% PVP and 40% Gelucire 44/14.

Young and coworkers successfully prepared spherical controlled release theophylline pellets by a hot-melt extrusion (HME) and spheronization process [4]. A powder blend of anhydrous theophylline, Eudragit® Preparation 4135 F, microcrystalline cellulose and polyethylene glycol 8000 powder was sieved, blended and then melt-extruded in a Randcastle Microtruder®. The hot-melt extruded pellets were prepared by first cutting a thin, extruded composite rod into symmetrical pellets. The pellets were then spheronized in a traditional spheronizer at elevated temperatures. The melt-extruded matrix pellets exhibited diffusion-controlled drug release. Drug release from the acrylic matrix system was influenced by the pH of the dissolution medium since the solubility of the matrix polymer, Eudragit® Preparation 4135 F, is pH dependent. The

surface morphology of the pellets was found to depend upon the spheronization parameters.

1.5.2 Tablets

Prapaitrakul and coworkers prepared disks using a melt extrusion method in which the molten materials were forced into a mold [86]. The disks contained glyceryl fatty acid esters (Gelucire), polyethylene glycol fatty acid esters, or a combination of the two with chlorpheniramine maleate as a model drug. The release of the drug into distilled water, pH 1.2 buffer, and pH 7.5 buffer exhibited square root of time dependence. An increase in the fatty acid ester hydrophilic-lipophilic balance (HLB) from 1 to 14 resulted in a 10-fold increase in the drug release rate. The maximum release rate was seen from the fatty acid ester with a melting point of 44°C. The pH of the dissolution medium had a minimal impact on the rate of drug release. The release rate was modified by blending Gelucires of different melting points and HLB values.

In a later study, these researchers prepared disks containing polyethylene, polycaprolactone, polyvinyl acetate, and cellulose acetate butyrate with theophylline as a model drug at a 50% loading [33]. The authors reported an 8 fold difference in the effective diffusion coefficient

between the various polymers. The effective diffusion coefficient increased 10-fold when the theophylline load was increased from 50 to 70% in the polycaprolactone and polyethylene disks. Disks with theophylline content greater than 70% by weight could not be made. The release rate was modified using soluble additives (sucrose, sodium chloride, Pluronic® and PEG).

Zhang and McGinity describe a novel method to prepare sustained release matrix tablets directly from a single screw hot-melt extruder [5, 9]. These researchers studied the properties of polyethylene oxide (PEO) as a drug carrier and studied the release mechanism of chlorpheniramine maleate (CPM) from matrix tablets. Large diameter rods (4.5 mm) were extruded and cut into tablets. PEG 3350 was included as a plasticizer to facilitate processing. The stability of the primary polymer, PEO, as a function of processing temperature was determined using gel permeation chromatography. The authors report that polymer type, temperature, and residence time in the extruder impacted the PEO stability. In addition, the researchers showed that additional mixing of the components occurred in the barrel of the extruder, since the content uniformity of the extruded tablets was within 99.0% to 101.0% of the theoretical content. As the

PEG 3350 concentration increased, the release of CPM from the extruded matrix tablets was found to increase. The rate of hydration and dissolution rate of the entire matrix system were thus accelerated due to the presence of the plasticizer. The rate of drug release was only slightly affected by changes in drug content until the drug loading reached 20%.

Crowley and coworkers studied the thermal stability of polyethylene oxide (PEO) in sustained release tablets prepared by hot-melt extrusion [7]. The weight average molecular weight of the polymer was determined using gel permeation chromatography. The chemical stability of PEO was found to be dependent on both the storage and processing temperature, and the molecular weight of the polymer. Storage of the polymer above its melting point significantly increased polymer degradation, and the degradation process was accelerated as the molecular weight of the polymer was reduced. The thermal stability of high molecular weight PEO (1,000,000 or PEO 1M) in sustained release chlorpheniramine maleate (CPM) tablets prepared by hot-melt extrusion was found to depend on the processing temperature and screw speed. Lower molecular weight PEO (100,000 or PEO 100K) was demonstrated to be a suitable processing aid for PEO 1M. Incorporation of PEO 100K reduced degradation of PEO 1M and did not alter the release rate of CPM. Vitamin E, Vitamin E Succinate

and Vitamin E TPGS were found to be suitable stabilizers for PEO, however, ascorbic acid was shown to degrade the polymer in solution. Thermal analysis demonstrated that Vitamin E Succinate and Vitamin E TPGS were dispersed at the molecular level in hot-melt extruded tablets. Solubilized Vitamin E Succinate and Vitamin E TPGS suppressed the melting point of the polyethylene oxide. Drug release rates from hot-melt extruded tablets stabilized with antioxidants were found to be dependent on the hydrophilic nature of the antioxidant.

Another unique application of the hot-melt extrusion technique is reported by Nakamichi and coworkers at Nippon Shinyaku Company [47]. The authors prepared a floating sustained release dosage form composed of nicardipine hydrochloride and hydroxypropyl methylcellulose acetate succinate using a twin screw extruder. Rods were extruded and then cut into tablets of different sizes. A dosage form with very small and uniform pores was obtained by selecting a screw that generated high pressure near the die, and by adjusting the processing temperatures. The authors demonstrated that the extruded, floating enteric polymer system was retained in the stomach for up to 6 hours.

1.5.3 Transdermal and Transmucosal Films

Currently, films for transdermal / transmucosal drug delivery and wound care applications are produced most frequently by casting from organic or aqueous solvents [10]. However, there are several problems with the casting technique. Gutierrez-Rocca and McGinity showed that physical aging of both aqueous and solvent cast acrylic films resulted in a decrease in elongation or elasticity and an increase film tensile strength [87]. This mechanical instability was related to the relaxation of the polymer chains as they moved toward a state of equilibrium. Also, it has been demonstrated that the type and level of plasticizers, curing time, and temperature have a significant effect on the dissolution rate of drugs from films formed from aqueous dispersions [88, 89].

Aitken-Nichol and coworkers investigated the viability of hot-melt extrusion technology in 1996 for the production of thin, flexible acrylic films for topical drug delivery [10]. The authors noted that the manufacturing process was not restricted by solvent concerns. The authors compared cast films with hot-melt extruded films. Eudragit® E100 was the primary thermoplastic polymer extruded. The authors reported that hot-melt extrusion was a viable technology for the production of free films of this acrylic resin. Although triethyl citrate was an acceptable

plasticizer for this polymer, these researchers found that lidocaine hydrochloride also plasticized for the acrylic films. The authors concluded that the differences in the dissolution rate and ductile properties between cast films and extruded films were due to the amount of drug dissolved in the polymer.

Repka and coworkers discussed the numerous disadvantages of solvent casting methods for preparing transdermal films [12]. These researchers produced hydroxypropylcellulose films using a Killion hot-melt extruder. Several plasticizers and two model drugs were incorporated into the HPC films. The influence of the plasticizers and drugs on the physical-mechanical properties of the films was investigated. The authors found that HPC films could not be produced without a plasticizer due to high torque levels on the extruder. All plasticizers examined in this study were found to be stable under the study processing conditions except PEG 400. The influence of processing temperature and storage time on the two model drugs (chlorpheniramine maleate and hydrocortisone) was also investigated. Chlorpheniramine maleate proved to be an excellent plasticizer for hydroxypropyl cellulose. The hot-melt extruded films were found to be mechanically and chemically stable for up to 12 months. The authors also reported that chlorpheniramine maleate was fully dissolved in

the hydroxypropyl cellulose film up to the 10% level. Hydrocortisone was also found to be a good plasticizer, however, its chemical stability was found to be a function of processing temperature and residence time in the extruder.

Repka, et al. also reported that the mechanical properties of the films depended on whether the testing was performed perpendicular to flow from the extruder or in the direction of flow from the extruder. All extruded films exhibited a decrease in tensile strength and a large increase in percent elongation when testing was performed perpendicular to flow versus in the direction of flow. These results were in contrast to those reported by Aitken-Nichol [10]. The cause of the discrepancy between the two studies is likely due to polymer compatibility between polyethylene and Eudragit E100 in the Aitken-Nichol study. However, these studies illustrate how “flow orientation” can impact the mechanical properties of hot-melt extruded delivery systems.

Repka and McGinity prepared films containing hydroxypropyl cellulose and polyethylene oxide by hot-melt extrusion with and without Vitamin E TPGS as a formulation additive [13]. Addition of 1, 3, and 5% Vitamin E TPGS decreased the glass transition temperature of the extruded films containing either a 50:50 or 80:20 ratio of HPC to PEO in

an almost linear fashion. The glass transition temperature of the film containing 3% Vitamin E TPGS was lowered by over 11ºC compared to the film without Vitamin E TPGS. The films containing 3% Vitamin E TPGS had similar mechanical properties to films containing 3% PEG 400, but a 3 fold increase in percent elongation was observed compared to films containing 3% triethyl citrate and 3% acetyltributyl citrate. Vitamin E TPGS also facilitated the processing of the HPC/PEO films by decreasing the barrel pressure, drive amps, and torque of the extruder.

Researchers at Johnson & Johnson disclose a bioadhesive hot-melt extruded film for intra-oral drug delivery [90]. These films may also be used for transmucosal drug delivery or transdermal systems. The films may be produced separately and layered after extrusion, or in some cases, a multi-layered system may be co-extruded in a continuous process. Currently, a marketed denture adhesive is prepared by hot-melt extrusion using thermoplastic polymers that adhere to the mucous membrane when wetted. A bioadhesive film has the benefit of simplifying dosage form design and reducing preparation costs, due to the elimination of the adhesive layer in the system. It is desirable for the film to have adequate adhesion strength so that retention of the film at the application site can be achieved.

Repka and McGinity conducted bioadhesion testing of hot-melt extruded hydroxypropyl cellulose films containing various additives on human subjects using a Chatillon testing apparatus [14]. These researchers found that force of adhesion, elongation at adhesive failure, and modulus of adhesion were a function of the type of additive in the extruded film. The force of adhesion was highest for the films containing carbomer (Carbopol® 971P) and polycarbophil (Noveon AA-1®). This study demonstrated that a single layer HPC film could be produced with the bioadhesive incorporated into the matrix, thus eliminating a separate "adhesive layer" and simplifying the process of transdermal and transmucosal delivery systems.

1.5.4 Implants

Rothen-Weinhold and coworkers prepared long-acting poly(lactic acid) implants containing vapreotide, a somatostatin analogue, by hot-melt extrusion [18]. Many peptides are susceptible to degradation and it is difficult to formulate and deliver them without significant loss of biological activity. Furthermore, the authors desired to deliver the peptide for a period of weeks in a controlled manner. However, the authors reported that the peptide degraded during manufacturing. The main

degradation product obtained after implant manufacturing was found to be a lactoyl lactyl-vapreotide conjugate. The researchers studied the influence of residual lactide in the polylactic acid on the formation of peptide impurities during manufacturing. This report illustrated how the purity of the carrier can impact the quality of the dosage form.

Melanotan-I (MT-I) release rates from biodegradable implants of poly(D,L lactide-co-glycolide) (PLGA) copolymer prepared by melt extrusion have been reported [19, 20]. The in-vitro release of MT-I exhibited a triphasic profile with an initial rapid release followed by a secondary phase of slow release, then a tertiary phase of rapid release due to erosion of the polymer. The initial rapid release observed with PLGA (50:50 molar ratio of lactic/glycolic acid) polymers was less than 5% of the drug load and the tertiary phase commenced after about 3 weeks. The factors controlling the drug release were polymer degradation and erosion which were controlled by the physical properties of the polymer such as molecular weight and viscosity.

A contraceptive vaginal ring containing polyethylene vinylacetate copolymers, etonogestrel and ethinyl estradiol was prepared by melt extrusion [48]. The powders were compounded in a twin-screw extruder, granulated and then spun into fibers. After leaving the extruder, the

strands were cooled to room temperature and granulated using a strand granulator. The steroids were completely dissolved in the polymer melt. A co-extrusion procedure was used to prepare the coaxial fibers in which two single screw extruders were connected to a spinning block. The molten polymers were delivered to two gear pumps which were necessary to provide precise flow control of both polymers to the spinneret. Finally, the membrane and core polymers were combined in the spinneret to form the coaxial fiber.

Implants composed of block copolymers have also been studied. Witt and coworkers investigated the degradation of ABA triblock copolymers, consisting of poly(lactide-coglycolide) A-blocks and poly(oxyethylene) B-blocks, and PLG, poly(lactide-co-glycolide), with respect to swelling behavior, molecular weight loss and polymer erosion. Implants were prepared by either compression molding or extrusion using a laboratory ram extruder. Insertion of an elastic B block did not lower the processing temperature, although the entanglement of the polymer chains was significantly reduced. In this report, the influence of implant geometry was found to be insignificant.

1.6 Quality Control and Regulatory Considerations

Pharmaceutical products prepared by hot-melt extrusion have been approved in the United States, Europe and Asia [91]. Comprehensive documentation of the process monitoring and control devices is easily accomplished. These parameters include feed rate, temperature, screw speed, pressure, melt viscosity, drive amperage and torque. Cleaning is accomplished by disassembly and removal of any excess material from the screw, barrel and die. These surfaces can then be swabbed and analyzed to satisfy cleaning validation requirements.

1.7 A View to the Future

Hot-melt extrusion technology is an attractive process for the manufacture of drug delivery systems. A wide range of dosage forms and applications from oral to topical and parenteral can be prepared. Solid dispersions and / or solid solutions of the drug embedded in the carrier matrices may allow for sustained release application and dissolution rate improvement. Solvents are not required and a broad selection of carriers and functional excipients are available.

High process temperatures and shear forces are the primary drawbacks of this process technology. However, these challenges can be overcome by formulation and engineering approaches. Selection of low melting carriers or the use of compatible plasticizers can reduce process temperatures. Extruder and screw design can also reduce the likelihood of drug or carrier degradation by reducing the shear forces or residence time. Given these considerations, even drugs known to be thermally labile can be processed.

Interest in hot-melt extrusion is increasing. The published literature reveals innovative and promising new approaches to drug delivery systems like effervescent granules, fast dissolving systems, complex formation and solid dispersions. This process allows for precise delivery of drug loads based upon the size and shape of the extrudate.

CHAPTER 2 RESEARCH OBJECTIVES

2.1 OVERALL OBJECTIVES

The objectives of this study were to investigate the properties of water soluble and water insoluble polymers as carriers for hot melt extruded dosage forms. The physicochemical and mechanical properties and the mechanisms of drug release of the hot-melt extruded dosage forms were also studied. The influence of processing conditions and formulation variables on the properties of hot-melt extruded dosage forms were also determined.

2.2 SUPPORTING OBJECTIVES

2.2.1 Investigate the Stability of Polyethylene Oxide in Matrix Tablets Prepared by Hot-Melt Extrusion

Hot-melt extrusion of a thermoplastic polymer is generally conducted at 15 – 60°C above the melting point of the polymer. During hot-melt extrusion, polymers are subject to mechanical, thermal and oxidative degradation. Mechanical degradation may be induced by the

shear effects imposed by the rotating screw. Thermal depolymerization results from high temperatures and includes random scission, scission from the ends of the polymer and unzipping of substitute groups. Oxidative degradation is the result of a chemical reaction between oxygen molecules and the polymer. Therefore, the thermal stability of PEO (MW = 1,000,000 or PEO 1M) in sustained release chlorpheniramine maleate tablets prepared by the hot-melt extrusion process was investigated. Gel permeation chromatography was used to determine the molecular weight of the polymer before and after hot-melt extrusion. The influence of processing conditions (temperature and screw speed) on polymer stability was studied. Low molecular weight PEO (MW = 100,000 or PEO 100K) was incorporated as a plasticizer to facilitate processing and antioxidants were included to stabilize the polymer. The influence of processing parameters and incorporation of a plasticizer and antioxidants on the drug release properties of the tablet was also investigated. Finally, the chemical stability of PEO under accelerated storage conditions (40ºC, 60ºC and 80ºC all at 75% relative humidity) was determined.

2.2.2 Characterize the Physicochemical Properties and Mechanism of Drug Release from Ethyl Cellulose Matrix Tablets prepared by Direct Compression and Hot-melt Extrusion

The physicochemical properties of the extruded dosage forms including drug release properties, crystalline properties, polymer-drug miscibility and polymer-drug interaction have been characterized using differential thermal analysis, X-ray diffraction and scanning electron microscopy. Since hot-melt extrusion is conducted at an elevated temperature, a crystalline drug substance can either be dispersed at the molecular level or dispersed as individual particles in the hot-melt extruded polymer matrix. The crystallinity of the drug substance following hot-melt extrusion is reported. The influence of the dissolved drug molecules on the thermal properties of the polymeric carriers will also be determined. Since the polymeric carrier is molten and pressurized inside the extruder, the hot-melt extrudate is anticipated to possess a lower porosity and higher tortuosity than tablets prepared by direct compression methods. A comparison of the physicochemical properties of dosage forms prepared by hot-melt extrusion with those prepared by direct compression technique has been conducted using a novel analytical

technique. Finally, the mechanism of drug release is related to the physical properties of the tablets.

2.2.3 Investigate the Influence of Guaifenesin and Ketoprofen on the Mechanical Properties of Hot-melt Extruded Polyethylene Oxide Films

The feasibility or producing transdermal and transmucosal films containing low molecular weight polyethylene oxide was investigated. Several transdermal systems use a polymeric carrier as a drug depot. However, little has been reported in the literature on the effect of the drugs on the physical and mechanical properties of the resultant films. In this study, guaifenesin and ketoprofen were selected to investigate their influence on the stability of hot-melt extruded polyethylene oxide films. The thermal properties of the hot-melt extruded films were investigated using differential scanning calorimetry. Scanning electron microscopy was used to examine the surface morphology of the films, and wide angle x-ray diffraction was used to investigate the crystalline properties of the polymer, drugs and physical mixtures and the solid state structure of the films. The stability of the polymer was studied using gel permeation chromatography. The mechanical properties, including percent elongation

and tensile strength of the films were determined on an Instron according to ASTM procedures.

CHAPTER 3 AN INVESTIGATION OF THE STABILITY OF POLYETHYLENE OXIDE IN MATRIX TABLETS PREPARED BY HOT-MELT EXTRUSION

* Reprinted with permission from Crowley, M. M., Zhang, F., Koleng, J. J., and McGinity, J. W., Biomaterials. **2002**, *23* (21), 4241-4248.

3.1 ABSTRACT

The thermal stability of polyethylene oxide (PEO) in sustained release tablets prepared by hot-melt extrusion was investigated. The weight average molecular weight of the polymer was studied using gel permeation chromatography. The chemical stability of PEO was found to be dependent on both the storage and processing temperature, and the molecular weight of the polymer. Storage of the polymer above its melting point significantly increased polymer degradation, and the degradation process was accelerated as the molecular weight was reduced. The thermal stability of PEO M_W = 1,000,000 (PEO 1M) in sustained release chlorpheniramine maleate (CPM) tablets prepared by

hot-melt extrusion was found to depend on the processing temperature and screw speed. Lower molecular weight PEO M_W = 100,000 (PEO 100K) was demonstrated to be a suitable processing aid for PEO 1M. Incorporation of PEO 100K reduced degradation of PEO 1M and did not alter the release rate of CPM. Vitamin E, Vitamin E Succinate and Vitamin E TPGS were found to be suitable stabilizers for PEO, however, ascorbic acid was shown to degrade the polymer in solution. Thermal analysis demonstrated that Vitamin E Succinate and Vitamin E TPGS were dispersed at the molecular level in hot-melt extruded tablets. Solubilized Vitamin E Succinate and Vitamin E TPGS suppressed the melting point of the polyethylene oxide. Drug release rates from hot-melt extruded tablets stabilized with antioxidants were found to be dependent on the hydrophilic nature of the antioxidant.

3.2 INTRODUCTION

Hydrophilic polymers have been used extensively to prepare sustained and modified release drug delivery systems. Several research groups have demonstrated the hot-melt extrusion technique [92] to be a viable method to prepare pharmaceutical dosage forms including granules

[2], pellets [3], sustained release tablets [5, 6] and transdermal drug delivery systems [10, 12, 14].

Dosage forms produced by the hot-melt extrusion method require a pharmaceutical grade thermoplastic material. Polyethylene oxide (PEO) is a free flowing, thermoplastic homopolymer synthesized by the heterogeneous catalytic polymerization of ethylene oxide monomer. It is commercially available in a wide range of molecular weights (100,000 to 8,000,000). PEO is miscible with water in all ratios due to hydration of the ether oxygen. PEO is a semi-crystalline polymer with a melting range of 57 – 73ºC.

PEO has been widely used to prepare sustained release dosage forms. Studies have shown that the high molecular weight PEO successfully delayed the release rate of soluble and insoluble drugs from matrix tablets prepared by direct compression [93, 94]. Apicella and coworkers [95] used PEO to produce buccal adhesive etofylline films by solvent casting methods. Stringer and Peppas [96] prepared cross-linked PEO hydrogels using gamma irradiation. Efentakis and Vlachou [97] incorporated PEO as the rate-controlling carrier in sustained release gelatin capsules with both soluble and insoluble model drugs. Zhang and

McGinity [5] investigated the drug release properties of sustained release tablets prepared by hot-melt extrusion techniques.

Few studies have been reported in the literature concerning the stability of polymers in sustained release matrix tablets prepared by hot-melt extrusion. During hot-melt extrusion, polymers are subject to mechanical, thermal and oxidative degradation. Mechanical degradation may be induced by the shear effects imposed by the rotating screw. Thermal de-polymerization results from high temperatures and includes random scission, scission from the ends of the polymer and unzipping of substitute groups. Oxidative degradation is the result of a chemical reaction between oxygen molecules and the polymer.

The objectives of the present study were to investigate the thermal stability of PEO (M_W = 1,000,000 or PEO 1M) in sustained release chlorpheniramine maleate tablets prepared by the hot-melt extrusion process. The influence of processing conditions on polymer stability was studied. Low molecular weight PEO (M_W = 100,000 or PEO 100K) was incorporated as a plasticizer to facilitate processing and antioxidants were included to stabilize the polymer. The influence of processing parameters and incorporation of a plasticizer and antioxidants on the drug release properties of the tablet was also investigated. Furthermore, the chemical

stability of PEO under accelerated storage conditions (40ºC, 60ºC and 80ºC all at 75% relative humidity) was determined.

3.3 MATERIALS AND METHODS

3.3.1 Materials

Polyethylene oxide resins were purchased from Union Carbide Corp. (Danbury, CT) and Polysciences, Incorporated (Warrington, PA). Vitamin E, Vitamin E acetate, Vitamin E Succinate, ascorbic acid, butylated hydroxyanisole, sodium perchlorate, triethylamine and chlorpheniramine maleate were purchased from Spectrum Chemical Co. (Gardena, CA). Vitamin E TPGS (D-α tocopheryl polyethylene glycol 1000 succinate) was supplied by Eastman Fine Chemicals (Kingsport, TN). Methanol was purchased from EM Science (Gibbstown, NJ). All materials were passed through a 20 mesh screen prior to use.

3.3.2 Thermogravimetric Analysis

Thermogravimetric analysis (TGA) was used to determine the thermal degradation temperature of the polymer. A Perkin-Elmer (Norwalk, CT) 7-series Thermogravimetrical Analyzer was used in this

study. Samples weighing approximately 20 mg were used for the analysis. Nitrogen of ultrahigh purity was used as the purging gas for the furnace chamber. The temperature ramp speed was set at 20°C per minute, and the percentage weight loss of the samples was monitored from 30°C to 900°C.

3.3.3 Molecular Weight Determination

Gel permeation chromatography was used to study the stability of the polymer by measuring its weight average molecular weight. All standards and samples were prepared at 0.5% w/w concentrations in mobile phase under gentle agitation on a radial shaker (Aberbach Corp, Ann Arbor, MI) for 12 hours and injected immediately. A Waters analytical system was used that included a WISP model 710B auto sampler (100µL sample injection volume), model 510 pump, Ultrahydrogel™ Columns (2000 and 1000 in series) and a model 410 differential refractometer as the detector. The data were collected using Millennium® Version 3.2 software. A third order calibration curve (R^2 = 0.99) was constructed using PEO standards (Polymer Standards Service, Silver Spring, MD) with peak molecular weights ranging from 4,450 to 1,700,000. The mobile phase was double-distilled water containing 0.1 M

sodium nitrate and was pumped at a flow rate of 0.8 ml/min. The columns were held at an operating temperature of 35°C during analysis. Injection precision was found to have a relative standard deviation of 1.5% for 10 injections.

3.3.4 Differential Scanning Calorimetry Analysis

Differential Scanning Calorimetry (DSC) was used to characterize the thermal properties of the polymer, drug and antioxidants in physical mixtures and hot melt extrudates. The DSC instrument was a model 2920 from TA Instruments (New Castle, DE). Ultrahigh purity nitrogen was used as the purge gas at a flow rate of 150 ml/min. Approximately 10 mg of sample was weighed and sealed in aluminum pans. The temperature ramp speed was 5°C per minute from 25°C to 150°C for all studies.

3.3.5 Hot-melt Extrusion Process

Prior to each run, the system was purged with polyethylene for 10 minutes followed by a 15 minute purge of PEO. The drug, polymer(s) and or antioxidants were geometrically diluted and introduced into a Robot Coupe High Shear Blender (Model RS1 3VG, Jackson, MS) and mixed at 2000 rpm for 3 minutes. The resultant blend was fed into a single-screw Randcastle Extruder (Model RC 0750, Cedar Grove, NJ) equipped with a

Nitralloy 135M screw (3:1 compression ratio with flight configuration containing feed, compression and mixing sections) and a rod shaped die (6 mm in diameter). The screw speed was either 10, 20, 40 or 60 rpm. The three heating zones and die temperatures were set and allowed to equilibrate. The residence time of the materials in the extruder was approximately 2 – 3 minutes. The extrudates were cooled to 45 – 55°C and manually cut into tablets weighing 250 mg.

3.3.6 In Vitro Release Properties

Dissolution testing was performed according to apparatus II of USP 24 on a Van Kel VK7000 Dissolution Tester (Van Kel Industries, Edison, NJ 08820) equipped with an auto sampler (Model VK 8000). The dissolution medium (900 ml of purified water) was maintained at 37°C (Model 750D) and agitated at 100 rpm. Samples (5ml) were removed at specified time points over a 12 hour period.

Samples were analyzed for CPM content using a Waters (Milford, MA) high performance liquid chromatography (HPLC) system with a photodiode array detector (Model 996) extracting at 261 nm. Samples were pre-filtered through a 0.45 μm membrane (Gelman Laboratory, GHP Acrodisc). A WISP® auto sampler (Model 710B) was used to inject 20μL

samples. The data were collected and integrated using Millennium® Version 3.2 software. The column was a Waters μBondapak™ C18 125Å (10 μm), 3.9 × 300 mm. The mobile phase contained a mixture of methanol: water: triethylamine in volume ratios of 675:325:2. The aqueous phase contained 0.71% w/w sodium perchlorate. The solvents were vacuum filtered through a 0.45 μm nylon membrane and degassed by sonication. The flow rate was 1.0 ml/min. The retention time of the CPM was 9 minutes. Linearity was demonstrated from 2 to 80 μg/ml (R^2 = 0.997) and injection repeatability was 0.38% Relative Standard Deviation (RSD) for 10 injections.

3.4 Results and Discussion

3.4.1 The Thermal Stability of PEO

The incorporation of oxygen into the backbone of an aliphatic chain polymer results in thermal instability since the C-O bond is less stable than a C-C bond [98]. When exposed to air or oxygen, PEO has been reported to oxidatively degrade in both bulk [99] and in solution [100]. This degradation has been reported to accelerate at elevated temperatures and upon exposure to ultraviolet light. In the present study, the thermal

depolymerization temperature of PEO was measured by thermogravimetric analysis. Depolymerization of polyethylene oxide was initiated at approximately 200°C. The main product of the PEO depolymerization process is smaller polymer segments.

The influence of storage temperature on the degradation of PEO 1M as measured by changes in weight average molecular weight is presented in Figure 3.1. The degradation rate of the polymer was faster under elevated storage temperatures. PEO is a semicrystalline polymer, essentially a two phase material consisting of spherulitic crystals embedded in an amorphous continuum. Maclaine and coworkers [101, 102] reported the crystallinity of PEO of molecular weight 1,000,000 to be in the range of 45 – 55% using dilatometry. Oxygen permeability of a polymer in the solid state increases with polymer chain mobility. Due to the highly ordered structure of the crystalline spherulites, the oxygen diffusion rate is significantly lower in the crystalline region than in the amorphous region [103].

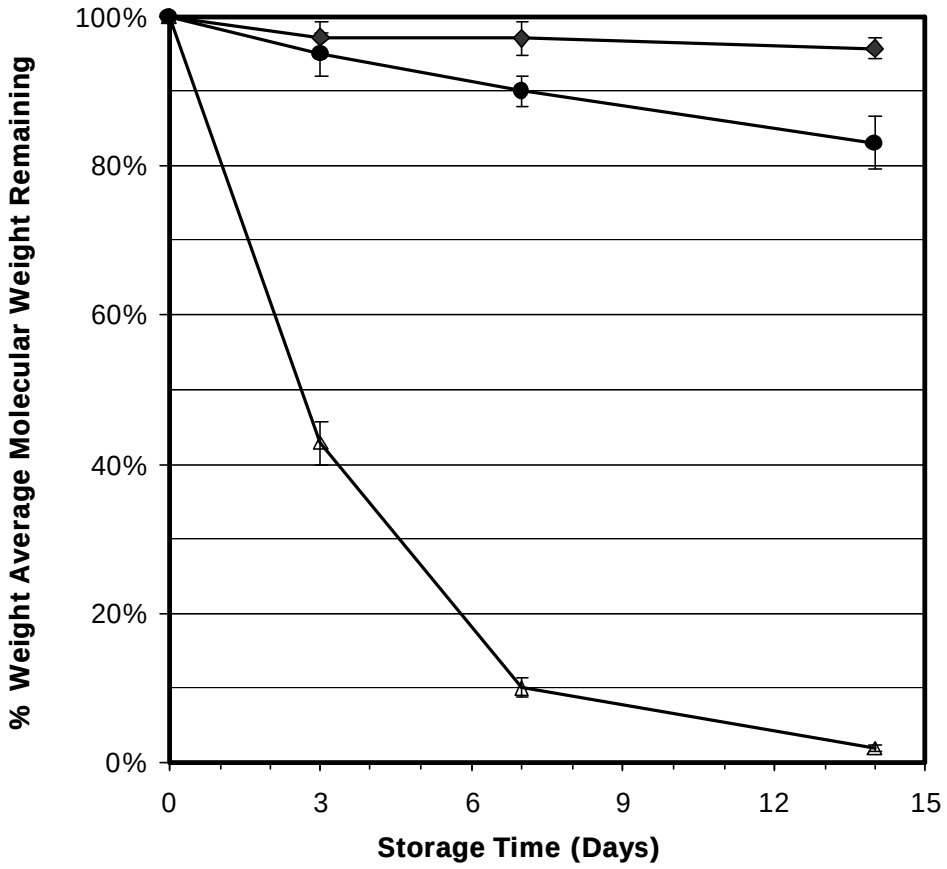

Figure 3.1: Influence of storage temperature on the weight average molecular weight of Polyethylene Oxide (PEO Mw = 1,000,000)

♦ 40°C • 60 °C Δ 80°C

Each point represents the mean ± standard deviation, n=3.

When PEO was stored below its melting point (range 55 – 80°C) at 40°C, or at 60°C, only the amorphous region and molten crystalline portions of the polymer are susceptible to oxidative degradation. When stored above its melting temperature at 80°C, both the crystalline and amorphous regions of the polymer are completely molten and the oxidative degradation of PEO was substantially accelerated. As polymer degradation accelerated, the physical appearance of the polymer changed, and when stored at 80°C for 14 days, PEO was soft and waxy with a distinctive odor.

The thermal oxidation of PEO was highly dependent on polymer molecular weight. The profiles in Figure 3.2 demonstrate that the lower molecular weight polymer degraded more rapidly than the higher molecular weight polymer (100,000 > 600,000 > 1,000,000). Maclaine and coworkers [101] reported the crystallinity of PEO reached a maximum at molecular weight 6,000 and decreased with increasing molecular weight. Because they are more crystalline, it was expected that low molecular weight polymer would be more resistant to thermal oxidation.

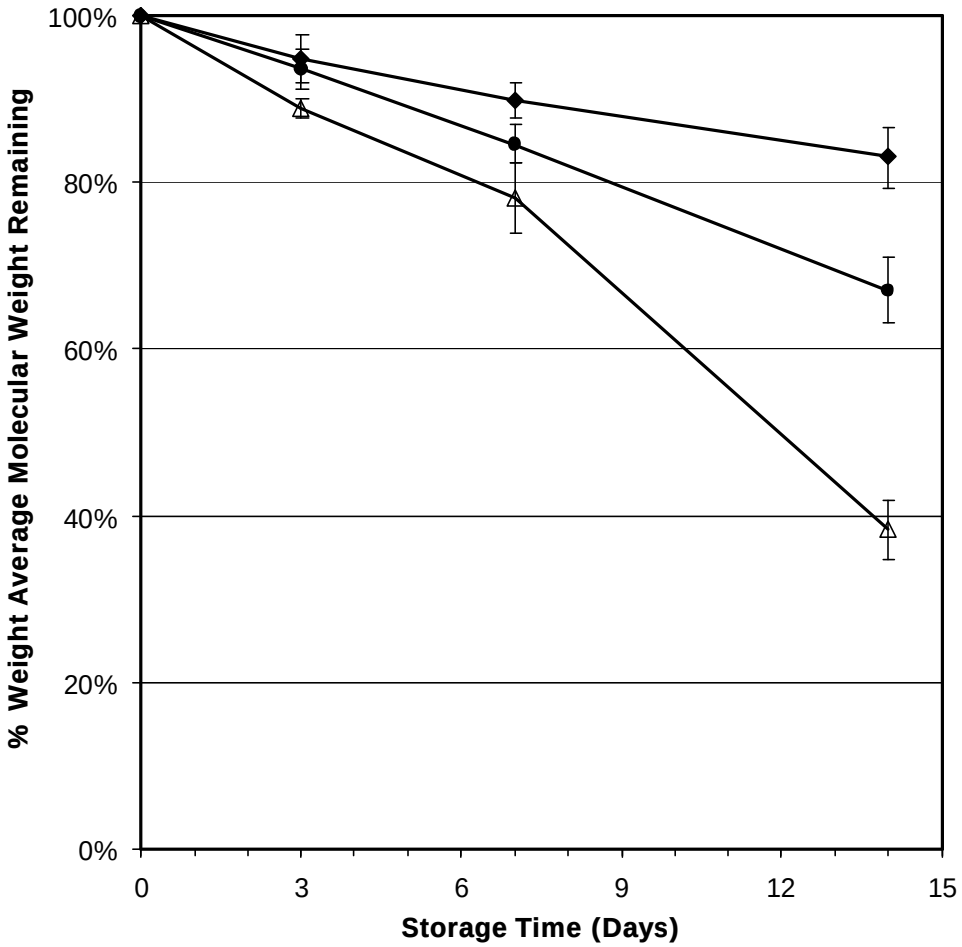

Figure 3.2: Relationship of polymer molecular weight in the thermal stability of Polyethylene Oxide when stored at 60°C, 75% relative humidity.

♦ 1,000,000, • 600,000 and Δ 200,000

Each point represents the mean ± standard deviation, n=3.

The melting point of a polymer crystal depends on its thickness, with smaller crystals melting at lower temperatures than larger crystals. Polymers are rarely crystallized to a uniform size and thus exhibit a melting range rather than a sharp melting point. The manufacturing process can also influence crystal size if the cooling rate and time are not tightly controlled.

Ozeki and coworkers [104] observed that the onset of melting and the melting point of PEO increased as the molecular weight increased. These results were confirmed in the present study. The DSC scan of PEO (1M) in Figure 3.3 reveals a melting range from 55 to 80°C. When stored at 60°C, smaller crystals that melt below 60°C are more susceptible to oxidative degradation. Thus, it can be concluded from this study that a higher proportion of small crystals are present in the lower molecular weight PEO.

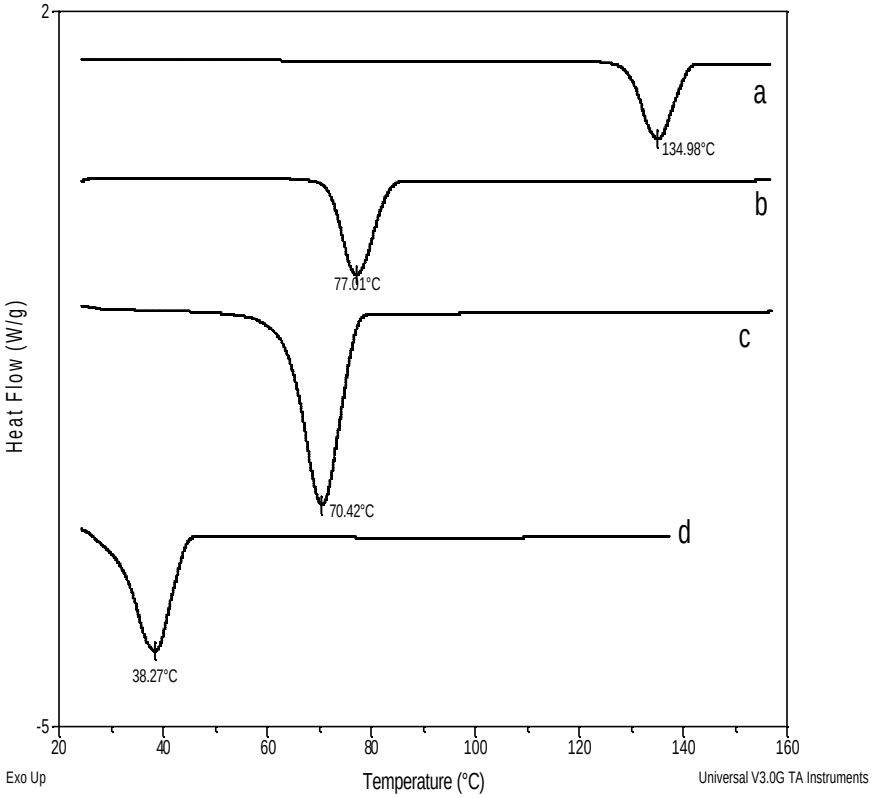

Figure 3.3: DSC profiles of the CPM, PEO and Antioxidants.

(a) CPM,

(b) Vitamin E Succinate

(c) PEO (Mw = 1,000,000)

(d) Vitamin E TPGS

3.4.2 The Hot-melt extrusion stability of PEO

The stability of PEO following hot-melt extrusion was investigated using a model formulation containing 20% chlorpheniramine maleate (CPM) and 80% PEO 1M. The influence of hot-melt processing on the weight average molecular weight of three different lots of PEO 1M was investigated. When extruded at 20 rpm and 70 – 105°C, the reduction in weight average molecular weight ranged from 8.2% to 11.3% for the three lots. The differences from one lot to another were not statistically significant ($n=6$, $\alpha=0.05$, $p>0.10$).

The influence of extrusion conditions on the weight average molecular weight of PEO is presented in Figure 3.4. At low screw speeds, polymer degradation increased with higher processing temperatures. These results suggest that thermal degradation rather than mechanical degradation was the dominant mechanism. Processing temperature and the transit time through the extruder were the parameters that significantly influenced the extent of PEO degradation. As screw speed was increased, polymer degradation decreased until melt fracture began to occur. The melt behavior of PEO has been reported to be

pseudoplastic in nature [105]. As the screw speed increased, the melt viscosity decreased due to shear thinning and the transit time through the extruder decreased. Melt fracture will occur when the polymer chains are forced to orient themselves in the die and recoil into a random configuration upon exit. At very high screw speeds, polymer degradation was due to both mechanical and thermal degradation.

Melt fracture was observed at the zone temperatures of 80, 90, 110, 120°C and a screw speed of 60 rpm, and at zone temperatures of 85, 100, 120 140°C and a screw speed of 80 rpm. Melt fracture was not observed at the lower temperature settings due to drive overload. These findings demonstrate that polymer stability can be modulated by process parameters and that high material throughput can be achieved.

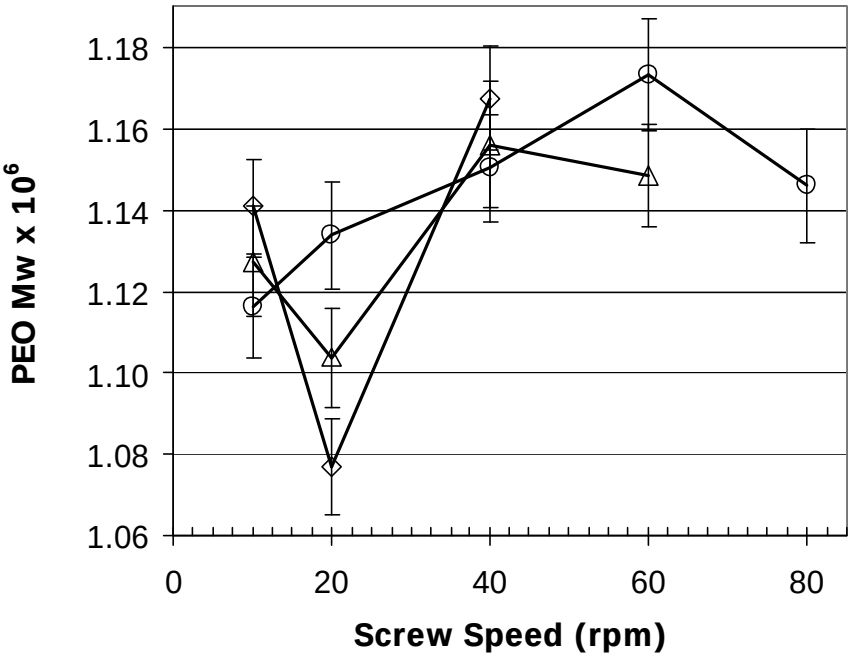

Figure 3.4: Influence of extrusion temperature & screw speed on the weight average molecular weight of PEO 1M (80% PEO 1M, 20% CPM).

◊ 70,80,100,105°C; Δ 80,90,110,120°C; and o 85,100,120,140°C

Each point represents the mean ± standard deviation, n=6.

Most extruders are supplied with an ammeter which indicates the load or current supplied by the drive motor to the screw in order to move the polymer through the extruder. The influence of processing temperatures and screw speed on drive amperage is presented in Figure 3.5. The drive amperage follows the same trends as polymer degradation at all three processing temperatures. At the processing conditions in which the polymer is more stable, the melt viscosity remained relatively high which created more resistance against the drive. As the polymer degrades, lower molecular weight chains are formed, melt viscosity is reduced and the drive amperage decreases. These findings demonstrate that drive amperage can be used as an indicator of polymer stability until melt fracture occurs. At the point of melt fracture, drive amperage decreased due to increased chain scission, in addition to relaxation and uncoiling of the polymer at the die exit.

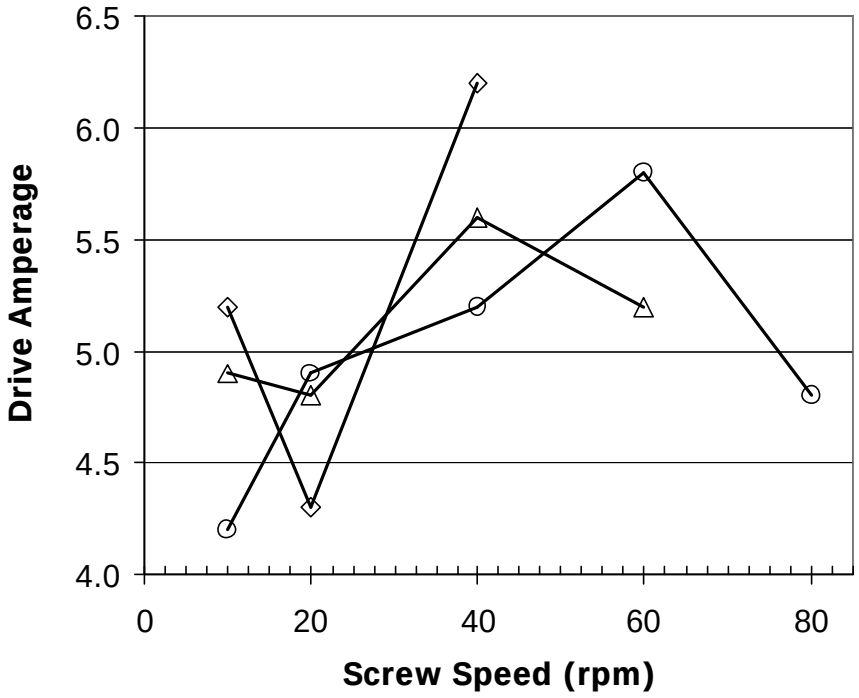

Figure 3.5: Influence of processing temperature & screw speed on drive amperage.

◊ 70,80,100,105°C; Δ 80,90,110,120°C; and o 85,100,120,140°C.

3.4.3 The Influence of Low Molecular Weight PEO

Low molecular weight PEO (M_w = 100,000) was investigated as a processing aid for the model formulation containing PEO 1M and CPM. The presence of PEO 100K reduced the melt viscosity, friction and chain entanglements between the PEO 1M molecules. As shown in Table 3.1, as the percentage of PEO 100K in the powder blend increased, the drive amperage decreased and the stability of PEO 1M increased.

In formulations A and B, the two different PEO polymers eluted as a single peak. However, formulation C, containing equal parts PEO 1M and PEO 100K eluted as two separate peaks. In this formulation, the weight average molecular weight of the PEO 100K polymer increased following extrusion. This demonstrates that degradation of PEO 1M during the extrusion process resulted in polymer chains with a weight average near 100,000. Thus, the additional PEO 100K formed during processing was shown to plasticize the parent polymer. This observation was confirmed by a reduction in drive amperage.

The in vitro release properties of formulations A, B and C are presented in Figure 3.6. The release rate of CPM from the extruded tablets was not significantly influenced by the presence of PEO 100K.

Although PEO 100K hydrates more rapidly and has a lower viscosity than PEO 1M, the rate of CPM diffusion through the swollen gel layer did not change substantially.

CPM was found to be stable under the extrusion conditions studied. There was no change in HPLC retention time for the extruded samples and the drug was completely recovered in the dissolution media.

Table 3.1: Extrusion Stability of PEO 1M and the Influence of PEO 100K on PEO Weight Average Molecular Weight as measured by Gel Permeation Chromatography.

	Formulation (%)			Pre Extrusion	Post Extrusion		Drive Current
	CPM	PEO 1M	PEO 100K	M_W ($\times 10^6$)	M_W ($\times 10^6$)	% Change	(Amps)
A	20	70	10	1.050 ± 0.028	0.958 ± 0.024	-8.8	2.9 – 3.2
B	20	60	20	0.912 ± 0.023	0.849 ± 0.025	-6.9	2.8 – 3.2
C	20	40	40	1.135 ± 0.016	1.084 ± 0.018	-4.5	2.4 – 2.6
				0.084 ± 0.005	0.093 ± 0.008	+10.7	

Unprocessed M_W: PEO (1M) M_W = 1.188 ± 0.024

Zone Temperatures: 70, 85, 100, 105°C
Screw Speed: 20 rpm

Values are reported as Average ± Standard Deviation, n=3.

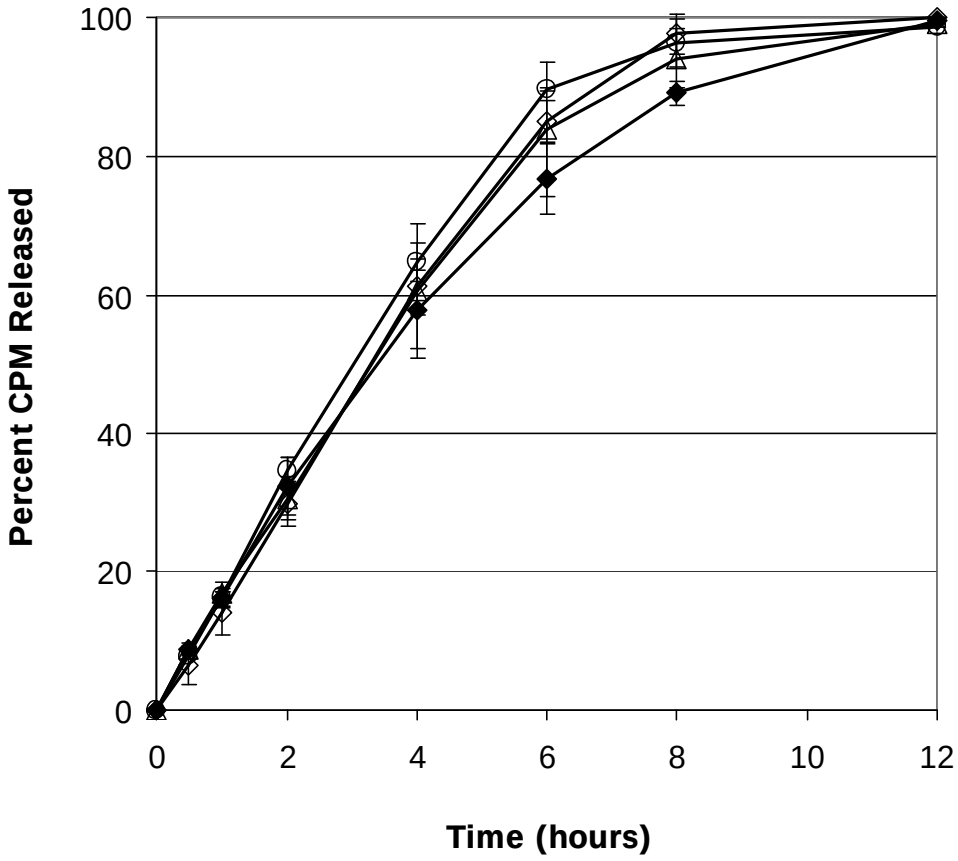

Figure 3.6: Influence of low molecular weight PEO on CPM release from hot-melt extruded tablets using USP Method II at 37°C and 100 rpm in 900 ml purified water.

♦ 20% CPM, 80% PEO 1M, 0% PEO 100K
Δ 20% CPM, 70% PEO 1M, 10% PEO 100K
◊ 20% CPM, 60% PEO 1M, 20% PEO 100K
o 20% CPM, 40% PEO 1M, 40% PEO 100K

Each point represents the mean ± standard deviation, n=6.

3.4.4 The Influence of Antioxidants

The thermal oxidation of PEO in the solid state has been characterized as an autocatalytic free radical process [99]. Antioxidants are often used to hinder oxidation reactions by scavenging free radicals. Antioxidants that have been used in pharmaceutical preparations include Vitamin E and its derivatives, Vitamin C (ascorbic acid) and butylated hydroxyanisole (BHA). Vitamin E TPGS is a water soluble derivative of natural Vitamin E. It is ampipathic and hydrophilic with surface active properties and has been used as an emulsifier, solubilizer and absorption enhancer. The influence of antioxidants on the hot-melt extrusion stability of PEO 1M matrix tablets containing CPM is presented in Table 3.2. The addition of 5% Vitamin E succinate, 1% Vitamin E and 30% Vitamin E TPGS successfully retarded molecular weight loss of PEO. The color of the extrudates was unchanged. These compounds have previously been found to suppress free radical production in photoirradiated pheolmelanin [106]. In contrast, Vitamin C and BHA did not stabilize PEO.

Table 3.2: Extrusion Stability of PEO 1M and the Influence of Antioxidants on PEO Weight Average Molecular Weight as measured by Gel Permeation Chromatography.

(20% CPM, 80 – x% PEO 1M and x% Antioxidant)

Formulation	Post Extrusion M_W ($\times 10^6$)	% Change	Drive Current (Amps)
No Antioxidant	0.836 ± 0.008	- 11.3	3.0 – 3.4
0.5% Vitamin E Succinate	0.828 ± 0.005	- 12.1	3.0 – 3.3
1.0% Vitamin E Succinate	0.867 ± 0.014	- 8.0	2.8 – 3.4
5.0% Vitamin E Succinate	0.917 ± 0.019	- 2.7	2.7 – 3.1
1.0% Vitamin E Acetate	0.828 ± 0.012	- 12.1	4.3 – 4.9
5.0% Vitamin E Acetate	0.826 ± 0.039	- 12.3	6.5 – 7.0
1.0% Vitamin E	0.916 ± 0.027	- 2.8	3.7 – 4.1
15.0% Vitamin E TPGS	0.843 ± 0.025	- 10.5	2.7 – 3.4
30.0% Vitamin E TPGS	0.907 ± 0.026	- 3.7	2.6 – 2.9
0.5% Ascorbic acid	0.730 ± 0.102	- 22.5	3.0 – 3.3
1.0% Ascorbic acid	0.626 ± 0.076	- 33.5	4.5 – 5.0
0.5% BHA	0.864 ± 0.013	- 8.3	3.4 – 3.7
1.0% BHA	0.874 ± 0.009	- 7.2	3.7 – 4.3
Unextruded PEO M_W 0.942 ± 0.021			

Zone Temperatures: 70, 85, 100, 105°C
Screw Speed: 20 rpm
Molecular weight values are reported as the mean ± standard deviation, n =3.

Both Vitamin E succinate and Vitamin E TPGS decreased the torque during extrusion suggesting an improvement in polymer chain motion. The miscibility of Vitamin E Succinate and Vitamin E TPGS in PEO was studied by DSC (Figure 3.7). The melting points of CPM, PEO 1M, Vitamin E TPGS and Vitamin E Succinate were found to be 135°C, 70°C, 38°C and 77°C, respectively. The melting point of Vitamin E TPGS can be observed in the thermograms of the physical mixtures. Thermograms of the extrudates containing Vitamin E succinate, 15% Vitamin E TPGS and 30% Vitamin E TPGS demonstrate a decrease in the melting point of PEO of approximately 9°C, 9°C and 10°C, respectively. Thermal transitions corresponding to the melting points of Vitamin E succinate and Vitamin E TPGS were not observed in the extrudates. These results demonstrate that both Vitamin E succinate and Vitamin E TPGS were miscible with PEO in the melt and when incorporated into the PEO crystals, the Vitamin E derivatives did not recrystallize after the extrudate cooled.

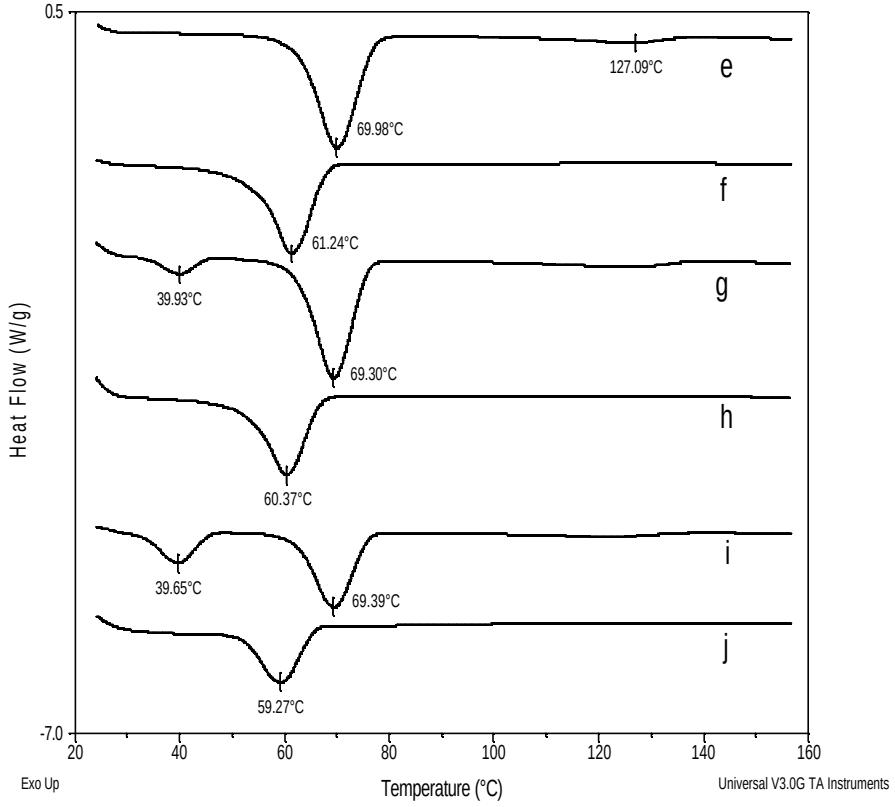

Figure 3.7: DSC profiles of the Physical Mixtures and Extruded Tablets.

(e) Physical mixture of 20% CPM, 75% PEO and 5% Vitamin E Succinate

(f) Hot-melt extrudate of 20% CPM, 75% PEO and 5% Vitamin E Succinate

(g) Physical mixture of 20% CPM, 65% PEO and 15% Vitamin E TPGS

(h) Hot-melt extrudate of 20% CPM, 65% PEO and 15% Vitamin E TPGS

(i) Physical mixture of 20% CPM, 50% PEO and 30% Vitamin E TPGS

(j) Hot-melt extrudate of 20% CPM, 50% PEO and 30% Vitamin E TPGS.

Both butylated hydroxyanisole and Vitamin E acetate were ineffective in stabilizing the molecular weight of PEO during extrusion. The torque during extrusion was significantly increased. It was anticipated that the oily nature of Vitamin E acetate would function as a thermal lubricant during the extrusion process. In general, suitable solvents for polymers will chemically and physically resemble the structural repeat units of the polymer. If this situation exists, the adhesive forces between the solvent and polymer are similar to the cohesive forces between solvent molecules or between polymer molecules. An exchange of a solvent molecule by a polymer structural unit occurs with little change in the adhesive and cohesive forces. In the case of poor or unsuitable solvents, the cohesive forces between polymer molecules are more favorable. If this situation exists, the polymer chain reduces its hydrodynamic radius.

Other researchers have reported that the acetate anion caused PEO to salt out of aqueous solution [105]. The results of our study suggested that the residual acetate anions in Vitamin E acetate reduced the polymer radius in the molten state, increasing chain entanglements and consequently, the load required to move the polymer through the extruder.

The appearance of extrudates containing ascorbic acid changed from white to brown within two hours. After extrusion, the molecular weight of PEO was considerably reduced and the polydispersity increased. McGary reported that strong acids reduced the solution viscosity of PEO [100]. Solutions of unprocessed PEO and ascorbic acid were prepared to examine whether the reduction in PEO molecular weight was the result of the extrusion process or a solution phenomenon (Table 3.3). The results from the solution study demonstrate that small quantities of ascorbic acid significantly reduced PEO molecular weight by an acid catalyzed chain scission reaction. However, it is also possible that the PEO degradation in solution with ascorbic acid is also accelerated by conditions during GPC analysis. It has been reported that ascorbic acid solutions undergo oxidation in the presence of air and are catalyzed by heat and traces of copper and iron [107].

Table 3.3: Influence of Ascorbic Acid on the Solution Stability of Polyethylene Oxide 1M as measured by Gel Permeation Chromatography.

Formulation % (w/w)			
PEO	Ascorbic Acid	M_W ($\times 10^6$)	% Change
100.0	0	1.241 ± 0.008	
99.9	0.10	1.119 ± 0.016	- 3.4
99.5	0.50	0.921 ± 0.038	- 25.8
99.0	1.00	0.788 ± 0.030	- 36.8
98.0	2.00	0.587 ± 0.019	- 52.8

Samples stored at 25°C for 12 hours.
Molecular weight values are reported as mean ± standard deviation, n=3.

The influence of the antioxidants on the release of CPM from extruded tablets and tablets prepared by direct compression is displayed in Figure 3.8. All extruded formulations displayed comparable release rates. The release of CPM from tablets prepared by direct compression was more rapid than those prepared by hot-melt extrusion due to the increase in porosity and a decrease in tortuosity in the tablet compact. The formulation containing 30% Vitamin E TPGS released CPM more rapidly than the other formulations. Vitamin E TPGS is amphiphillic and can influence the release rate of CPM in two ways. Although the waxy, hydrophobic portion of the molecule can hinder the penetration of water into the tablet core, the hydrophilic portion of the molecule can reduce the gel strength of the PEO matrix and increase erosion during dissolution. In this case, the latter is the dominant factor. The formulation containing 1% Vitamin E released CPM more slowly than all other formulations. The hydrophobic nature of Vitamin E delayed the penetration of water into the PEO matrix, resulting in a slower rate of gel hydration and formation.

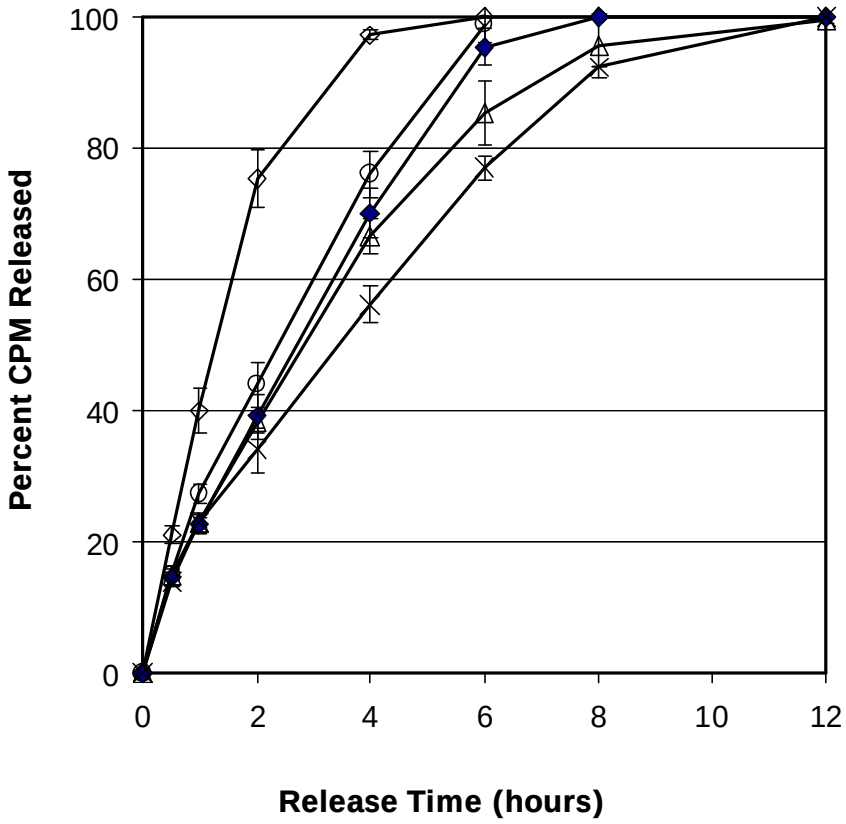

Figure 3.8: Influence of antioxidants on the release of CPM from tablets using USP Method II at 37°C and 100 rpm in 900 ml purified water.

◊ 20% CPM, 80% PEO 1M, Direct Compression

o 20% CPM, 50% PEO 1M, 30% Vitamin E TPGS Extrudate

♦ 20% CPM, 75% PEO 1M, 5% Vitamin E Succinate Extrudate

Δ 20% CPM, 80% PEO 1M Extrudate

X 20% CPM, 79% PEO 1M, 1% Vitamin E Extrudate

Each point represents the mean ± standard deviation, n=6.

3.5 CONCLUSIONS

The results of this study demonstrated that the thermal stability of PEO was dependent on both the storage temperature and the molecular weight of the polymer. Storage of the polymer above its melting point significantly increased its degradation. Polymer degradation when stored below its melting point is due to oxygen permeation in the amorphous region of the polymer.

PEO matrix tablets prepared by hot-melt extrusion were sensitive to both process temperature and screw speed. The mechanism of polymer degradation during extrusion is both thermal and mechanical. At very high screw speeds, degradation is due to melt fracture. The amperage consumed by the extruder motor drive can be used as an indicator of polymer stability.

The addition of PEO 100K improved processing of PEO 1M and did not significantly influence the rate of CPM release from matrix tablets. Vitamin E, Vitamin E succinate and Vitamin E TPGS were found to be suitable stabilizers for PEO during processing. Vitamin E succinate and Vitamin E TPGS were dispersed at the molecular level in hot-melt extruded tablets. Ascorbic acid was shown to degrade the polymer in solution.

Drug release rates from hot-melt extruded tablets stabilized with antioxidants were dependent on the hydrophilic nature of the antioxidant.

3.6 ACKNOWLEDGEMENTS

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CHAPTER 4 CHARACTERIZATION OF THE PHYSICOCHEMICAL PROPERTIES AND MECHANISM OF DRUG RELEASE FROM ETHYL CELLULOSE MATRIX TABLETS PREPARED BY DIRECT COMPRESSION AND HOT-MELT EXTRUSION

4.1 ABSTRACT

The objective of this research project was to determine the physicochemical properties and investigate the drug release mechanism from ethyl cellulose matrix tablets prepared by either direct compression or hot-melt extrusion of binary mixtures of water soluble drug (guaifenesin) and the polymer. Ethyl cellulose was separated into "fine" or "coarse" particle size fractions corresponding to 325 - 80 mesh and 80 - 30 mesh particles, respectively. Tablets containing 30% guaifenesin were prepared at 10 kN, 30 kN, or 50 kN compaction forces and extruded at processing temperatures of 80 – 90°C and 90 – 110°C. The drug

dissolution and release kinetics were determined and the tablet pore characteristics, tortuosity, thermal properties and surface morphologies were studied using helium pycnometry, mercury porosimetry, differential scanning calorimetry and scanning electron microscopy. The tortuosity was measured directly by a novel technique that allows for the calculation of diffusion coefficients in 3 experiments. The Higuchi diffusion model, percolation theory and polymer free volume theory were applied to the dissolution data to explain the release properties of drug from the matrix systems. The release rate was shown to be dependent on the ethyl cellulose particle size, compaction force and extrusion temperature.

4.2 INTRODUCTION

Ethyl cellulose (EC) is a nontoxic, stable, compressible, inert, hydrophobic polymer that has been widely used to prepare pharmaceutical dosage forms. The properties of ethyl cellulose sustained release products including film coated tablets [108], microspheres [109, 110], microcapsules [111] and matrix tablets for both soluble and poorly soluble drugs [112, 113] have been reported.

Hot-melt extrusion (HME) is a widely used process in the plastics industry to produce tubing, pipes and films. In pharmaceutical systems, HME has been used to prepare granules, sustained-release tablets, and transdermal drug delivery systems [3, 5, 6, 114, 115]. It has been demonstrated that the processing method can dictate the porosity and pore structure of the dosage form [116, 117]. Previous workers have also shown that thermal processing results in a more tortuous product [118, 119].

Several researchers have suggested that diffusion controlled sustained release dosage forms prepared by HME have slower drug release rates than those prepared by traditional methods due to lower porosity and higher tortuosity [4]. Polymeric materials are softened or molten during hot-melt extrusion and subjected to intense mixing resulting in the generation of high pressures. Air present in the powder bed can be excluded from the polymer melt during hot-melt extrusion. As a result, HME dosage forms are expected to have a lower porosity and higher tortuosity, in comparison with the dosage forms prepared by tabletting processes.

The Higuchi Square Root Model [120] has been successfully applied to model the kinetics of drug release from matrix systems. The equation

(4.1) was derived from Fick's Law of Diffusion and applied to porous hydrophobic polymeric drug delivery systems in homogenous matrices and granular matrices.

$$Q(t) = \sqrt{D_s C_a \frac{e}{t}(2C_o - eC_a)t} = \sqrt{D_{app} C_a (2C_o - eC_a)t} = k\sqrt{t} \qquad \text{(Equation 4.1)}$$

In equation 4.1, Q(t) represents the cumulative amount of drug released at time t per unit surface area, D_s denotes the drug diffusion coefficient in the release medium, C_o is the total amount of drug in the matrix, C_a is the solubility of the drug in the release media, ε is the porosity, τ is the tortuosity of the matrix, D_{app} is the apparent or observed diffusion coefficient ($D_{app} = \frac{D_s e}{t}$) and k is the dissolution rate constant. Drug release can be manipulated by varying: (a) the initial concentration of drug within matrix; (b) porosity; (c) tortuosity; (d) polymer system forming the matrix; and (e) the solubility of the drug.

Drug release from a porous, hydrophobic polymeric drug delivery system occurs when the drug comes into contact with the dissolution media, subsequently dissolves and diffuses through media filled pores. Thus, geometry and structure of the pore network are important in this process [121, 122]. The Higuchi model has been reported to fail at drug

loading levels below the percolation threshold [6]. Below the percolation threshold, incomplete drug release is observed presumably due to limited accessibility of many drug particles to the dissolution medium since they are encapsulated by water insoluble polymeric materials.

The objectives of the present study were to determine the physicochemical properties of ethyl cellulose matrix tablets prepared by either direct compression or hot-melt extrusion in order to explain the drug release mechanism. The influence of compaction force and processing temperature on drug release rates and the physical properties of the tablets was studied. The effect of ethyl cellulose particle size was examined in tablets prepared by both direct compression and hot-melt extrusion. The median pore size, porosity and tortuosity of the matrix tablets prepared by the two techniques were determined using the Webb technique allowing calculation of the diffusion coefficients.

4.3 THE THEORY OF MERCURY INTRUSION POROSIMETRY AND TORTUOSITY

Knowledge of tortuosity is necessary to determine diffusion coefficients from observed dissolution data. Researchers have relied upon secondary

methods to determine tortuosity. These techniques required several steps and were time intensive. Recently, a novel approach using mercury intrusion porosimetry for direct measurement of tortuosity was reported [123]. Mercury intrusion porosimetry has been used to study the pore characteristics of tablets [116, 124, 125], granules [117, 126], ceramic particles for sustained drug delivery [127] and excipients [128]. The technique is based upon the unique properties of mercury. Mercury behaves as a non-wetting liquid toward most substances and will not penetrate a solid unless pressure is applied. For circular pore openings, the Washburn equation (4.2) [129] relates the applied pressure, P, and the radius, r, of the pores intruded with a non-wetting liquid:

$$r = \frac{-2\gamma \cos\theta}{P} \qquad \text{(Equation 4.2)}$$

where γ is the surface tension of mercury and θ is the contact angle between the liquid and sample. The inverse relationship between pore radius and applied pressure indicates low pressures are used to measure large pore sizes and high pressures are used to measure small pore sizes.

Katz & Thompson [130, 131] introduced an expression (4.3) for determination of permeability in porous rocks from mercury intrusion curves based upon concepts from Percolation Theory [132, 133]. These

researchers found that absolute permeability, K, was related to the rock conductivity at a characteristic length L_c.

$$K = \frac{L_{max}}{89 \cdot L_c} f S(L_{max}) \qquad \text{(Equation 4.3)}$$

Equation 4.3 requires determination of the length at which conductance is at a maximum, L_{max}, and the fraction of total porosity, ϕ, filled at this length $S(L_{max})$. The characteristic length, L_c, is the length at which mercury spans the entire sample and was found to be the point at which percolation begins. It is determined at the point of inflection in the rapidly rising region of the cumulative intrusion curve. Several different scientific disciplines have used the Katz-Thompson method to determine permeability in a variety of materials [134-138].

Jörgen Hager also derived an expression for material permeability based upon a capillary bundle model and knowledge of material tortuosity [139]. The capillary bundle model describes the pore network as homogenously distributed in random directions. Using the Hagen-Poiseuille correlation for fluid flow in cylindrical geometries in combination with Darcy's Law, Hager was able to derive an equation (4.4) for permeability, K in terms of total pore volume, V_{tot}, material density, ρ,

pore volume distribution by pore size, $\int_{h=r_{c,\min}}^{h=r_{c,\max}} h^2 f_v(h)\,dh$ and material tortuosity, τ. In this method, Hager obtained all parameters except tortuosity from mercury intrusion porosimetry analysis.

$$K = \frac{r}{24\tau^2(1 + rV_{tot})} \int_{h=r_{c,\min}}^{h=r_{c,\max}} h^2 f_v(h)\,dh \qquad \text{(Equation 4.4)}$$

Webb concluded that combining the Hager and Katz-Thompson expressions (equation 4.5) provided a means for determining tortuosity from mercury intrusion porosimetry data [123, 140].

$$\tau = \sqrt{\frac{r}{24(1 + rV_{tot})} \int_{h=r_{c,\min}}^{h=r_{c,\max}} h^2 f_v(h)\,dh} \qquad \text{(Equation 4.5)}$$

Since the determination of tortuosity depends upon permeability, changes in material permeability during the analysis will affect the reported value for tortuosity. Webb also reported that improved accuracy was achieved using true density data from helium pycnometry. Thus, the Webb technique allows determination of tortuosity from only two experiments, helium pycnometry and mercury intrusion. The apparent diffusion coefficient and diffusion coefficient can then be calculated using the rate constant from dissolution studies.

4.4 MATERIALS AND METHODS

4.4.1 Materials

Guaifenesin and Glacial Acetic Acid were purchased from Spectrum Laboratory Products (Gardenia, CA). Ethyl cellulose grade S10 was kindly donated by the Dow Chemical Company (Midland, MI). Methanol was purchased from EM Science (Gibbstown, NJ).

4.4.2 Methods

4.4.2.1 Preparation of Tablets

Ethyl cellulose was sieved into two fractions. The "coarse" fraction included the material that passed through a 30 mesh screen and was retained by an 80 mesh screen. The "fine" fraction included material that passed through 80 mesh screen and was retained on a 325 mesh screen. Guaifenesin was passed through a 30 mesh screen prior to use. The ethyl cellulose particle size fractions were confirmed by laser light scattering using a Malvern Mastersizer S (Malvern Instruments Limited, Malvern, Worcestershire, UK).

A model formulation containing 30% guaifenesin and 70% ethyl cellulose was selected for this study. The drug and polymer were

geometrically diluted in a glass mortar and pestle and then introduced into a V Blender (Blend Master®,Patterson-Kelley, East Stroudsburg, PA) and mixed for 15 minutes. Tablets were prepared from the resultant blend by either direct compression or via hot-melt extrusion.

4.4.2.2 Direct Compression Process

Tablet compacts were prepared using a Carver 25 ton laboratory press (Fred Carver, Menomonee Falls, WI) and a 6 mm diameter flat faced punch and die set. The force applied on the punches was measured using a load cell (ISI Inc., Round Rock, TX) mounted directly on the press with strain gauge sensors. Tablets weighing 250 ± 5 mg were compressed to 10 kN, 30 kN or 50 kN for 3 seconds and ejected from the die.

4.4.2.3 Hot-Melt Extrusion Process

The powder blend was fed into a single-screw Randcastle Extruder (Model RC 0750, Cedar Grove, NJ) equipped with a Nitralloy 135M screw (3:1 compression ratio with flight configuration containing feed, compression and mixing sections) and a rod shaped die (6 mm in diameter). The screw speed was 20 rpm. The three heating zones and die temperatures were set and allowed to equilibrate. Extrusion samples were prepared using two different processing temperature ranges: “low”

(80, 85, 85, 90°C) and “high” (90, 105, 105, 110°C). The residence time of the materials in the extruder was approximately 2 – 3 minutes. The extrudates were cooled to 45 – 55 °C and manually cut into tablets weighing 250 ± 5 mg.

4.4.2.4 In Vitro Release Properties

Dissolution testing was performed using apparatus II on a Van Kel VK7000 Dissolution Tester (Van Kel Industries, Edison, NJ 08820) equipped with an auto sampler (Model VK 8000) according to the guaifenesin tablet monograph in USP 24. Six tablets were placed into the dissolution medium (900 ml of purified water) which was maintained at 37°C by a circulating bath (Van Kel Model 750D) and agitated at 50 rpm. Samples (5ml) were removed at specified time points over a 12 hour period without media replacement.

Samples were analyzed for guaifenesin content using a Waters (Milford, MA) high performance liquid chromatography (HPLC) system with a photodiode array detector (Model 996) extracting at 276 nm. Samples were pre-filtered through a 0.45 μm membrane (Gelman Laboratory, GHP Acrodisc). An auto sampler (Model 717plus) was used to inject 20μL samples. The data were collected and integrated using

Empower® Version 5.0 software. The column was an Alltech Alltima™ C_{18} 3 μm, 150 × 4.6 mm. The mobile phase contained a mixture of water:methanol:glacial acetic acid in volume ratios of 600:400:15. The solvents were vacuum filtered through a 0.45 μm nylon membrane and degassed by sonication. The flow rate was 1.0 ml/min. The retention time of the guaifenesin was 4 minutes. Linearity was demonstrated from 2 to 200 μg/ml (R^2 = 0.997) and injection repeatability was 0.35% relative standard deviation for 10 injections.

4.4.2.5 True Density by Helium Pycnometry

The true density of the powder formulations and tablets was determined in triplicate using helium pycnometry (Micrometrics® AccuPyc 1330 Pycnometer; Norcross, GA). Twelve tablets were placed in a 12 cm^3 sample cup and purged twenty times at 19.85 psi followed by six analytical runs at 19.85 psi. The equilibration rate was 0.0050 psi/minute. An equivalent mass of the powder mixtures was measured in the same manner.

4.4.2.6 Mercury Intrusion Porosimetry

The bulk density and tortuosity of the tablets were determined using an Autopore IV 9500 mercury intrusion porosimeter (Micromeritics,

Norcross, GA). Incremental volumes of mercury were plotted against pore diameters according to the Washburn equation (4.2). A surface tension value of 485 dynes/cm was used for mercury and its contact angle was 130°. Twelve tablets were placed in #5 bulb penetrometer and pressure was applied from 1 to 15,000 psia, representing pore diameters of 0.012 – 360 μm. The pressure at each point was allowed to equilibrate for 10 seconds. Each run was performed in triplicate. Tablets were analyzed prior to and post dissolution, with the removal of water from the tablets following dissolution by drying to a constant weight under vacuum for a minimum of 72 hours.

4.4.2.7 Percent Effective Porosity Determination

Percent effective porosity, ε was determined according to the Varner technique [141] using equation (4.6) in which ρ_t is the true density of the tablet as determined by helium pycnometry and ρ_b is the bulk density as determined by mercury intrusion porosimetry. Three runs of twelve tablets were analyzed first by helium pycnometry followed by mercury intrusion porosimetry.

$$e = \frac{r_t - r_b}{r_b} \qquad \text{(Equation 4.6)}$$

4.4.2.8 Modulated Differential Scanning Calorimetry Analysis

Temperature modulated differential scanning calorimetry (M-DSC) was used to characterize the thermal properties of the polymer and drug in physical mixtures and hot melt extrudates. M-DSC analysis was conducted using a Thermal Advantage Model 2920 from TA Instruments (New Castle, DE) equipped with Universal Analysis 2000 software. Ultrahigh purity nitrogen was used as the purge gas at a flow rate of 150 ml/min. The sample was weighed to 10 ± 5 mg and placed in aluminum pans (Kit 0219-0041, Perkin-Elmer Instruments, Norwalk, CT) and crimped with an aluminum lid. The temperature ramp speed was 2°C per minute from 25°C to 150°C for all studies with a modulation rate of 1.592°C every minute.

4.4.2.9 Scanning Electron Microscopy

Scanning electron microscopy was used to study the surface morphology of the hot-melt extruded tablets. The samples were mounted on an aluminum stage using adhesive carbon tape and placed in a low humidity chamber for 12 hours prior to analysis. Samples were coated with gold-palladium for 60 seconds under an argon atmosphere using a Pelco® Model 3 Sputter Coater (TED Pella, Inc., Tusin, CA, USA) in a high

vacuum evaporator equipped with an omni-rotary stage tray. Scanning electron microscopy was performed using a Hitachi S-4500 field emission microscope operating at an accelerating voltage of 15 kV and a 15 μA emission current. Images were captured with Quartz® software.

4.4.2.10 Statistical Analysis

One-way analysis of variance (ANOVA) was used to determine statistically significant differences between results. Results with p values < 0.05 were considered statistically significant ($\alpha = 0.05$). Dissolution curves were analyzed by the model independent approach of Moore and Flanner for dissolution curve comparison using the similarity (f1) and difference factors (f2) [142].

4.5 Results & Discussion

4.5.1 The Influence of Ethyl Cellulose Particle Size on Drug Release

The influence of ethyl cellulose particle size and processing conditions on the release rate of guaifenesin from matrix tablets was studied. The influence of ethyl cellulose particle size, compaction force and extrusion temperature on guaifenesin release rate is presented in

Figure 4.1 and Figure 4.2. The guaifenesin release rate from the matrix was highly dependent upon ethyl cellulose particle size and the processing conditions employed to prepare the tablet. In both cases, slower release rates were observed with small particle size ethyl cellulose.

According to Percolation Theory, when a matrix is composed of a water soluble drug and a water insoluble polymer, drug release occurs by dissolution of the active ingredient through capillaries composed of interconnecting drug particle clusters and the pore network [143, 144]. As drug release continues, the interconnecting clusters increase the pore network through which interior drug clusters can diffuse. The total number of ethyl cellulose particles increases when its particle size is reduced. With more ethyl cellulose particles present, the theory predicts that fewer clusters of soluble drug substance are formed. Furthermore, the presence of finite drug clusters (encapsulated drug particles) is more statistically plausible. The resulting pore network becomes less extensive and more tortuous resulting in slower drug release.

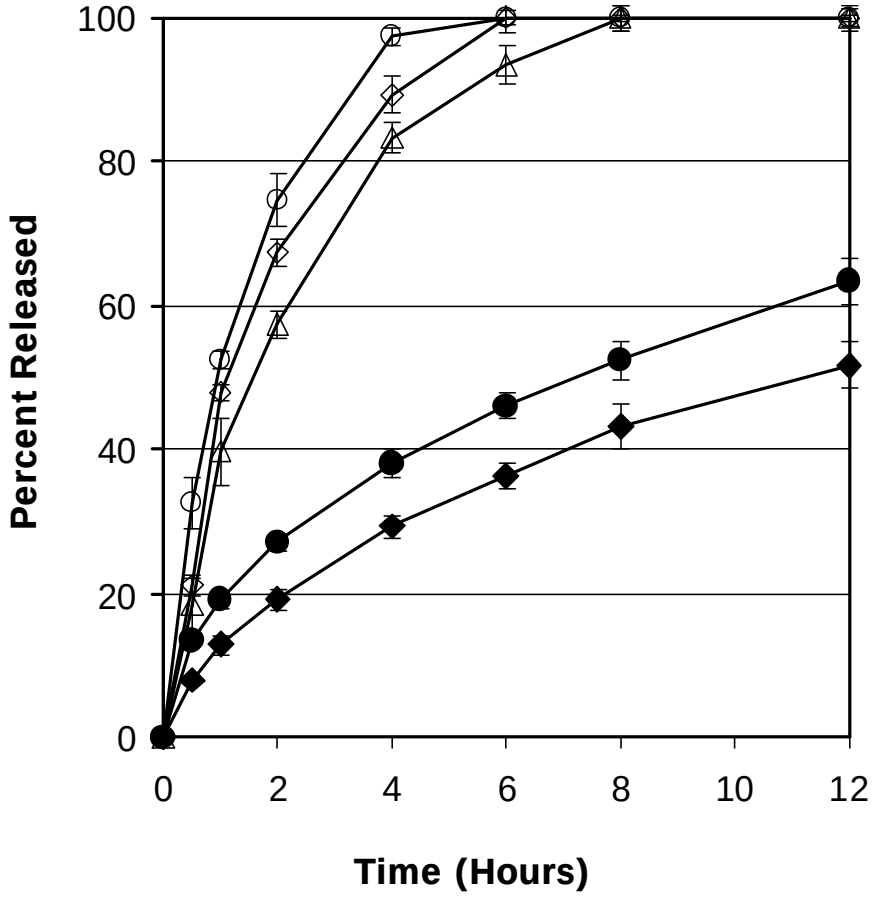

Figure 4.1: Influence of ethyl cellulose particle size, compaction force and extrusion temperature on guaifenesin release from matrix tablets prepared by direct compression and hot-melt extrusion.

Matrix Tablets Prepared Using "Fine" Ethyl Cellulose (325 – 80 Mesh)

- o Direct Compression, 10 kN
- ◊ Direct Compression, 30 kN
- ∆ Direct Compression, 50 kN
- • Hot-Melt Extrusion, 80, 85, 85, 90°C
- ♦ Hot-Melt Extrusion, 90, 105, 105, 110°C

Each point represents the mean ± standard deviation, n = 6.

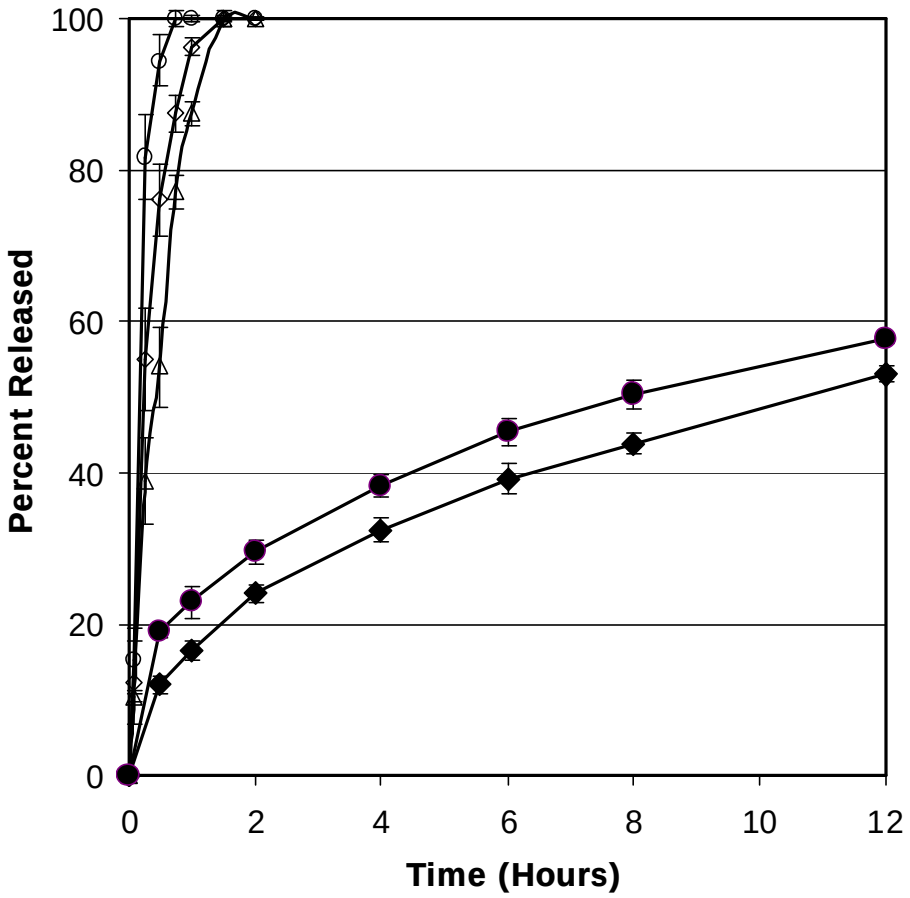

Figure 4.2: Influence of ethyl cellulose particle size, compaction force and extrusion temperature on guaifenesin release from matrix tablets prepared by direct compression and hot-melt extrusion.

Matrix Tablets Prepared Using "Coarse" Ethyl Cellulose (80 – 30 Mesh)

- o Direct Compression, 10 kN
- ◊ Direct Compression, 30 kN
- ∆ Direct Compression, 50 kN
- • Hot-Melt Extrusion, 80, 85, 85, 90°C
- ♦ Hot-Melt Extrusion, 90, 105, 105, 110°C

Each point represents the mean ± standard deviation, n = 6.

Mercury porosimetry and helium pycnometry were used to determine the pore characteristics and tortuosity of the tablets prior to dissolution testing. The median pore radius, percent effective porosity and tortuosity of the matrix tablets are presented in Table 1. Statistically significant differences in median pore radius ($n = 3$, $p < 0.006$), porosity ($n = 3$, $p < 0.02$) and tortuosity ($n = 3$, $p < 0.009$) were observed between matrix tablets prepared with "fine" and "coarse" ethyl cellulose particle sizes. The median pore radius was smaller, the tablets less porous and more tortuous when prepared with "fine" ethyl cellulose (137 – to 529 Å, 0.4 – 4.1% porosity and 4.7 – 321 tortuosity) than in tablets prepared with "coarse" ethyl cellulose (351 to 1439 Å, 0.7 to 6.5% porosity and 1.3 – 125 tortuosity). These data are supported by the dissolution results.

Katikaneni and coworkers [145-148] reported that pseudoephedrine hydrochloride release from ethyl cellulose matrix tablets prepared by direct compression was controlled by ethyl cellulose particle size and compression force. These authors concluded that the drug release rate decreased due to a reduction in porosity and increased matrix tortuosity at high compaction forces or when a finer particle of size ethyl cellulose was used. The findings in the present study confirm the work of Katikaneni, support the predictions of Percolation Theory and demonstrate

the utility of the mercury porosimetry technique for determination of tortuosity.

Generally, pore radii greater than 200 Å are necessary to avoid hindered diffusion [149]. Hindered diffusion can be due to steric exclusion or hindered particle motion. In these situations, either the pore radii are sufficiently small that the molecular dimensions of the solute restrict its diffusion or excessive frictional resistance is created. Hindered diffusion is typically observed when values of the particle radius to pore wall radius ratio are greater than 0.1. The molecular dimensions of guaifenesin were modeled using SAVOL3 software to assess the likelihood of hindered diffusion (Figure 4.3) [150]. Assuming a spherical shape, guaifenesin was found to have a radius of 3.53 Å excluding a solvent radius and 5.44 Å with a solvent radius. Assuming an ovoid shape and including a solvent radius, the model predicted the major axis to be 7.84 Å, the first minor axis to be 6.13 Å and the second minor axis to be 3.89 Å. Thus, the minimum guaifenesin particle radius to pore radius ratio is 0.04 in the case of the hot-melt extruded tablets prepared using “fine” ethyl cellulose and processed at 90 – 110°C. This value is sufficiently small that hindered diffusion can be considered negligible.

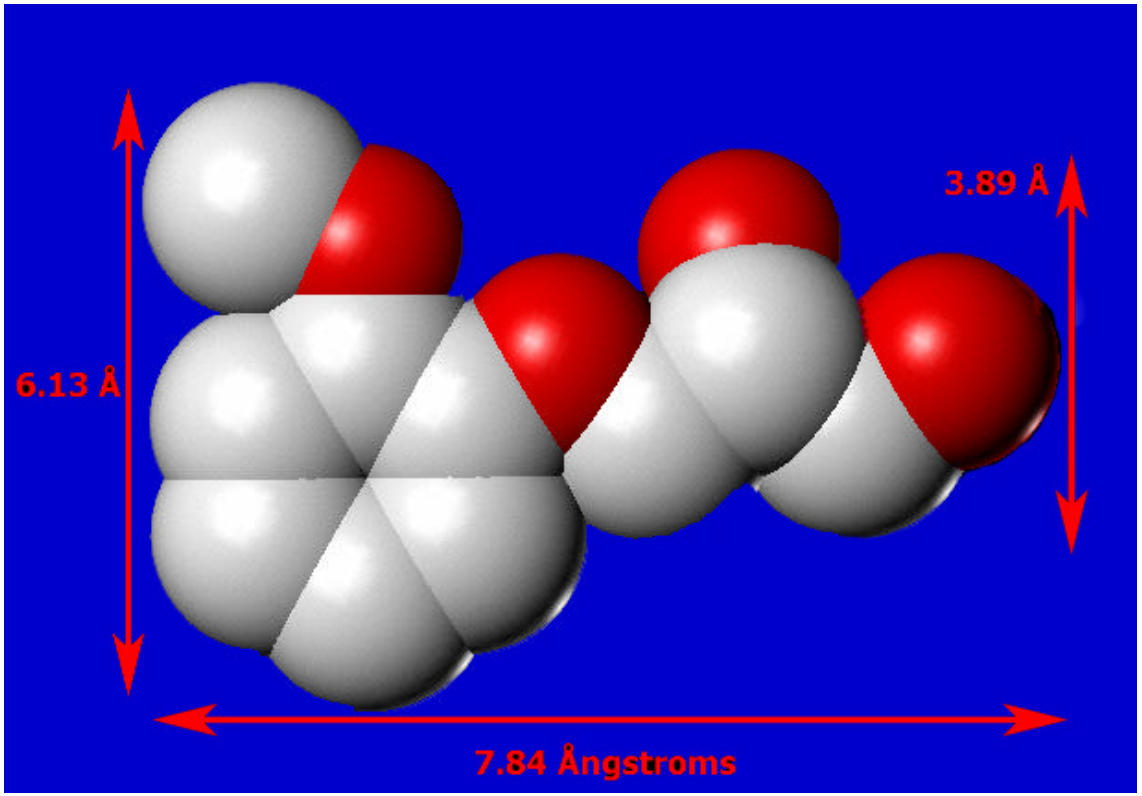

Figure 4.3: 3-Dimensional image of the molecular dimensions of Guaifenesin using SAVOL3 software.

Table 4.1: Median pore radius, % porosity and tortuosity of matrix tablets prepared by direct compression (DC) and hot-melt extrusion (HME) containing 30% guaifenesin and 70% ethyl cellulose measured before and after dissolution testing.

Processing Conditions	Median Pore Radius (Å)		% Porosity		Tortuosity	
	Before	After	Before	After	Before	After
"Fine" Ethyl Cellulose (325 – 80 mesh)						
DC 10 KN	529 ± 24		4.1 ± 0.3		4.7 ± 1.1	
DC 30 KN	476 ± 26		3.8 ± 0.2		6.0 ± 0.6	
DC 50 KN	475 ± 17		3.1 ± 0.2		6.9 ± 0.9	
HME 80, 85, 85, 90°C	264 ± 8	575 ± 51	1.0 ± 0.2	8.1 ± 1.8	53.2 ± 8.1	4.7 ± 0.6
HME 90, 105, 105, 110°C	137 ± 6	521 ± 65	0.4 ± 0.2	7.8 ± 2.2	321 ± 22	5.2 ± 0.9
"Coarse" Ethyl Cellulose (80 – 30 mesh)						
DC 10 KN	1439 ± 42		6.5 ± 0.2		1.3 ± 0.7	
DC 30 KN	906 ± 23		5.7 ± 0.3		2.1 ± 0.6	
DC 50 KN	710 ± 25		5.2 ± 0.2		2.8 ± 0.5	
HME 80, 85, 85, 90°C	392 ± 11	642 ± 48	2.3 ± 0.4	8.7 ± 1.4	41.8 ± 5.5	4.4 ± 0.3
HME 90, 105, 105, 110°C	351 ± 13	588 ± 57	0.7 ± 0.1	8.0 ± 1.1	125 ± 16	5.0 ± 1.1

Each point represents the mean ± standard deviation, n = 3.

Several assumptions are made using the mercury porosimetry technique which can introduce considerable error into the measurements. The assumption of circular pore cross sections or "cylindrical pore geometry" is due to mathematical convenience in order to avoid complexities calculating mean radii and contact angles in irregularly shaped pores. As a result, the technique is biased to calculate smaller pore sizes than are actually present. Furthermore, "ink bottle pores" also bias the pore size calculation to the small side. Ink bottle pores are defined as pores in which the diameter increases as one moves to its inner dimensions [151, 152]. Mercury intrusion also involves subjecting the tablets to equal pressures from 360° as the mercury is forced inside. This means that as mercury intrudes into the pores, the walls of pores penetrated by mercury at a given pressure are uniformly affected by the same pressure. This makes collapse of a pore wall unlikely. However, the tablet can compress under the applied pressure which allows for additional mercury to intrude. This also biases measurement to calculation of smaller than actual pore size. Obviously, the compression of ethyl cellulose is a concern using this technique. To minimize the impact of tablet compression, the applied pressure was not allowed to exceed

that applied during the direct compression experiments (50 kN or 15,000 psia). Despite these limitations, pore size information obtained from mercury porosimetry experiments has been consistently demonstrated to be representative.

4.5.2 The Influence of Tableting Technique on Drug Release

Guaifenesin release rates were considerably slower in tablets prepared by hot-melt extrusion than those prepared by direct compression as shown in Figure 4.1 and Figure 4.2. Statistically significant differences in median pore radius ($n = 3$, $p < 0.006$), percent effective porosity ($n = 3$, $p < 0.002$) and tortuosity ($n = 3$, $p < 0.0004$) were observed between the direct compression and hot-melt extruded tablets as shown in Table 1. The median pore radius was smaller and the tablets less porous when prepared by hot-melt extrusion (137 – 392 Å, 0.4 – 2.3% porosity and 41.8 – 321 tortuosity) than by direct compression (475 – 1439 Å, 3.1 – 6.5% porosity and 1.3 – 6.9 tortuosity). Adsorption and binding studies did not reveal any interactions. Complete drug recovery was obtained in samples dissolved in ethanol. Thus, the differences in release rate are due to the bonding mechanism of the particles in the two tableting techniques. Ethyl cellulose has been reported to be ductile and the

predominant mechanism during compaction is plastic deformation [146]. During hot-melt extrusion, solid bridges are formed upon cooling.

The extrusion temperatures were above the melting point of guaifenesin but below the glass transition temperature of ethyl cellulose. The molten drug can act as a solvent for the polymeric particles. Polymeric particles that do not go into solution are softened at elevated temperatures and deformed by the rotating screw during extrusion. Upon cooling, extensive solid bridges are formed between the particles resulting in a smaller pore radius and more tortuous network. These results demonstrate that densification of the molten mass during extrusion occurs to a greater extent relative to compaction of the powder during compression.

Thermal treatment of amorphous polymers has also been shown to decrease polymer free volume [2]. Elevated temperatures and high pressures during hot-melt extrusion followed by cooling significantly impact the free volume. Polymer chain motion and free volume increase with temperature allowing molten guaifenesin molecules to enter these voids. Upon cooling, the guaifenesin molecules remain dispersed in these domains. The net effect is an increase in the degree of packing and a reduction in free volume. Diffusion of molecules through amorphous

polymers is governed by free volume and packing. Thus, a decrease in drug transport is anticipated when the free volume decreases and packing order increases.

The miscibility of guaifenesin in ethyl cellulose was studied by modulated differential scanning calorimetry. The glass transition temperature of ethyl cellulose was found to be 129.3°C (Figure 4.4, A) and the melting point of guaifenesin was found to be 85.6°C (Figure 4.4, B). The melting point of guaifenesin can be observed in the thermograms of the physical mixtures (Figure 4.4, C & F). Thermograms of the hot-melt extrudates processed at 80 - 90°C show a weak melt transition about 9°C below the melting point of guaifenesin (Figure 4.4, D & G). Strong thermal transitions corresponding to the melting point of guaifenesin are not observed in the extrudates processed at 90 – 100°C (Figure 4.4, E & H). These results suggest that guaifenesin was miscible with ethyl cellulose while in the molten state and did not recrystallize after cooling.

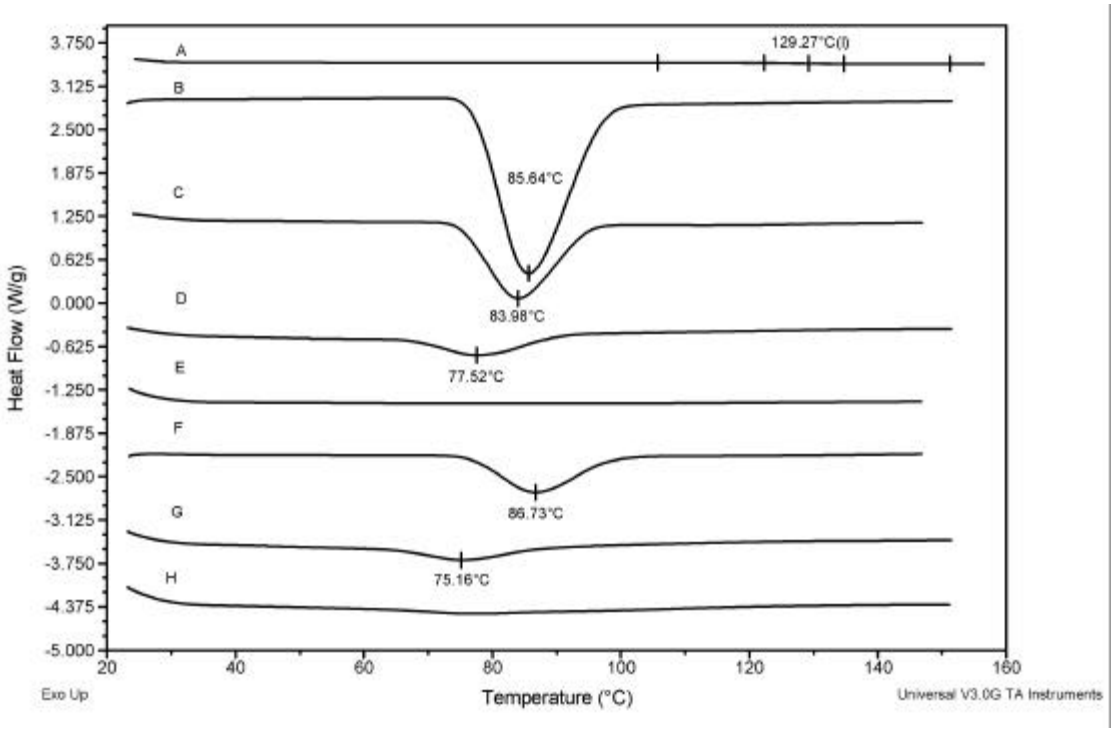

Figure 4.4: Modulated differential scanning calorimetry profiles of ethyl cellulose, guaifenesin, physical mixtures and hot-melt extrudates.

A. Ethyl cellulose
B. Guaifenesin
C. Physical mixture of 30% guaifenesin and 70% “Coarse” ethyl cellulose
D. Hot-melt extrudate of 30% guaifenesin and 70% “Coarse” ethyl cellulose processed at 80, 85, 85, 90°C
E. Hot-melt extrudate of 30% guaifenesin and 70% “Coarse” ethyl cellulose processed at 90, 105, 105, 110°C
F. Physical mixture of 30% guaifenesin and 70% “Fine” ethyl cellulose
G. Hot-melt extrudate of 30% guaifenesin and 70% “Fine” ethyl cellulose processed at 80, 85, 85, 90°C
H. Hot-melt extrudate of 30% guaifenesin and 70% “Fine” ethyl cellulose processed at 90, 105, 105, 110°C

4.5.3 The Influence of Compaction Force on Drug Release

The release rate of guaifenesin decreased with increasing compaction force in tablets prepared by direct compression (Figures 4.1 & 4.2). At higher compaction forces, the powder bed densifies to a greater extent and eliminates more of the air in the powder bed and voids in individual particles. The increased densification process results in a tablet with greater mechanical strength, lower porosity and higher tortuosity. These results were confirmed by the helium pycnometry and mercury porosimetry measurements (Table 4.1). The median pore radius and percent effective porosity decreased and tortuosity increased as the compaction force was raised.

4.5.4 The Influence of Hot-Melt Extrusion Temperature on Drug Release

The guaifenesin release rate in hot-melt extruded tablets decreased as the extrusion temperature increased. Guaifenesin release rates from matrix tablets extruded at 80 – 90°C were statistically different from those prepared at 90 – 110°C, according to the model independent approach (f1 = 29.3 and f2 = 30.6). Statistically significant differences in median pore radius ($n = 3$, $p < 0.01$), percent effective porosity ($n = 3$, $p < 0.0002$)

and tortuosity ($n = 3$, $p < 0.002$) were observed between tablets prepared at the two extrusion temperatures. The median pore radius was larger, the tablets more porous and tortuous when extruded at 80 – 90°C (264 – 392 Å, 1.0 – 2.3% porosity and 41.8 – 53.2 tortuous) than when extruded at 90 – 110°C (137 – 351 Å, 0.4 – 0.7% porosity and 125 – 321 tortuous).

Modulated differential scanning calorimetry revealed small melting transitions in the extrudates processed at low temperatures (Figure 4.4, D & G). These thermal events were absent in the extrudates processed at higher temperatures suggesting that a molecular dispersion was formed to a greater extent at higher extrusion temperatures. Since both processing temperatures were above the melting point of guaifenesin but below the glass transition temperature of ethyl cellulose, it is likely guaifenesin dissolved the ethyl cellulose particles more readily at higher temperatures. The resulting solid dispersion was less porous and more tortuous than that formed at lower processing temperatures.

The stability of polymers used in hot-melt extrusion has been previously investigated [3, 6, 7, 13]. The stability of ethyl cellulose during hot-melt extrusion by measuring molecular weight using gel permeation

chromatography has been described [2, 32, 153, 154]. These researchers report that ethyl cellulose molecular weight was stable during extrusion within the processing conditions employed in this study. Degradation of ethyl cellulose was observed at high temperatures. The onset of degradation of ethyl cellulose was found to occur at ~190°C and discoloration at temperatures above 205°C.

Scanning electron microscopy was used to investigate the surface morphology of the hot-melt extruded matrix tablets prior to dissolution testing and the data are presented in Figures 4.5 – 4.9. The surface morphology of the hot-melt extruded tablets was found to depend upon extrusion temperature. At low extrusion temperatures, individual particles are visible (Figures 4.5 and 4.7). These particles are likely responsible for the weak melting transitions observed in the DSC experiments (Figure 4.4, D & G). Few particles and pores are visible and the tablet surface was found to have a striated appearance (Figure 4.6 and 4.8) when processed at higher processing temperatures. The striated appearance is the result of "rifling" or shearing of the molten mass on the die wall upon exit from the extruder (Figure 4.9).

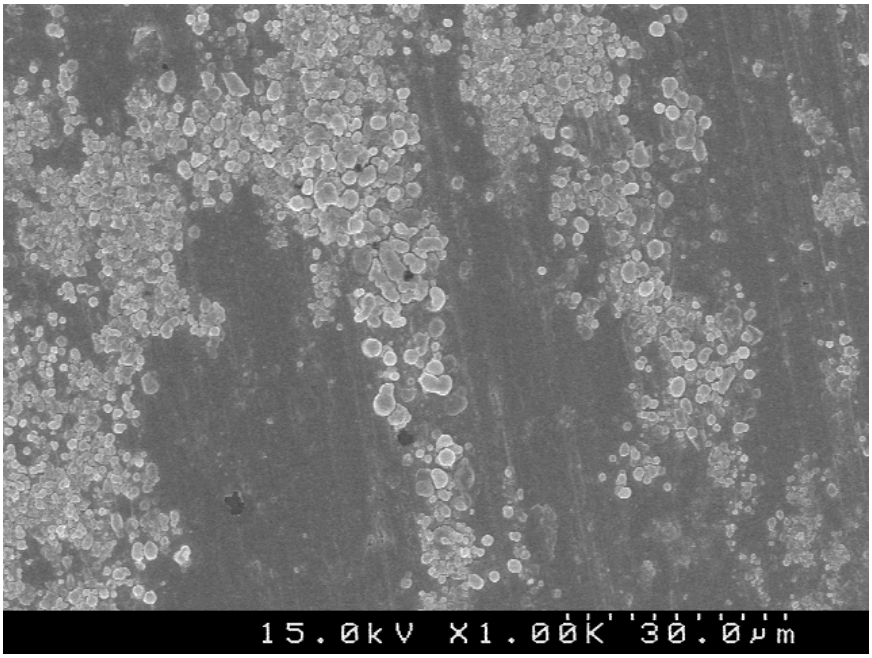

Figure 4.5: SEM micrographs of the surface of hot-melt extruded matrix tablets containing 30% guaifenesin and 70% “Fine” ethyl cellulose processed at 80, 85, 85, 90°C viewed at 1,000 X magnification.

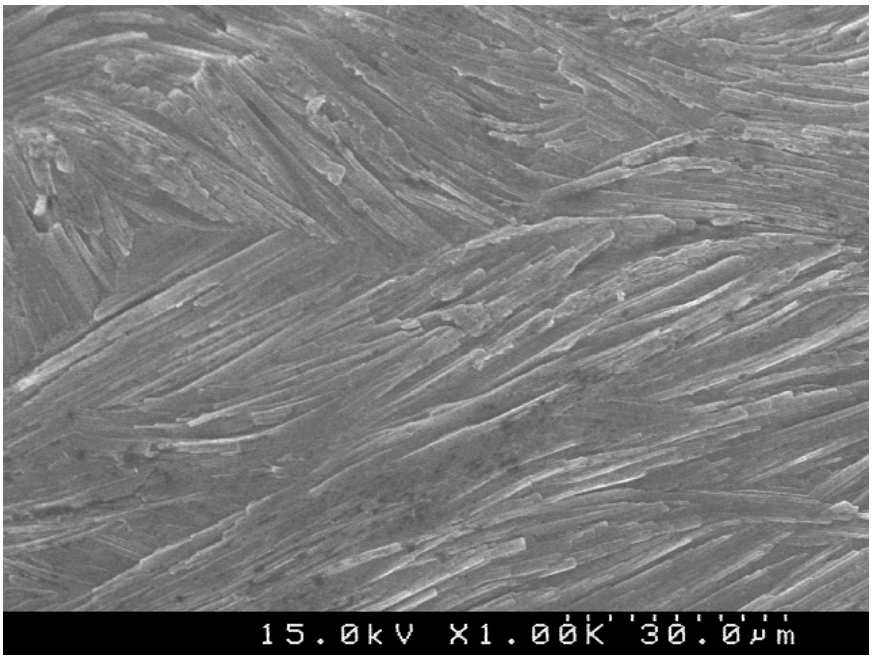

Figure 4.6: SEM micrographs of the surface of hot-melt extruded matrix tablets containing 30% guaifenesin and 70% “Fine” ethyl cellulose processed at 90, 105, 105, 110°C viewed at 1,000 X magnification.

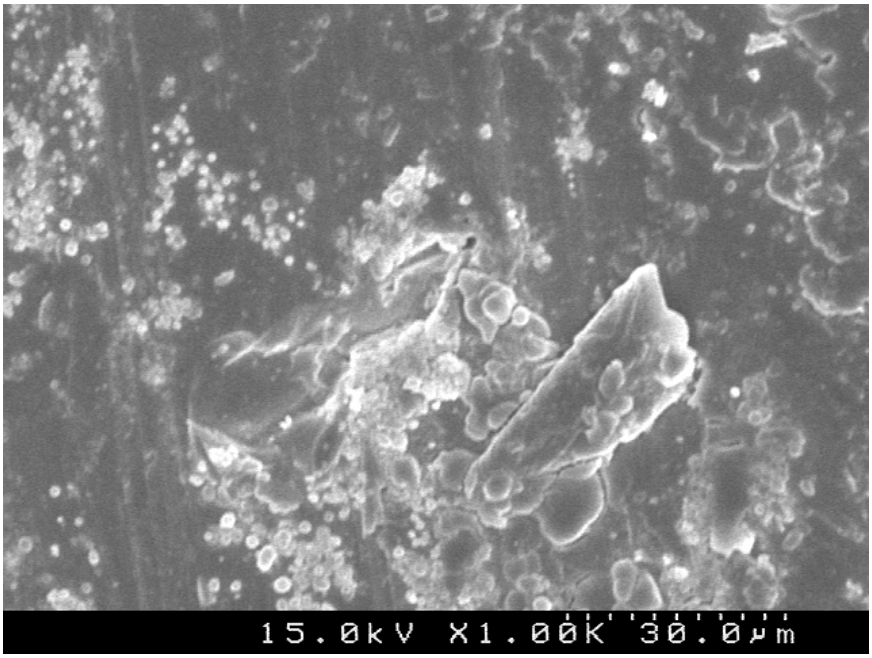

Figure 4.7: SEM micrographs of the surface of hot-melt extruded matrix tablets containing 30% guaifenesin and 70% “Coarse” ethyl cellulose processed at 80, 85, 85, 90°C viewed at 1,000 X magnification.

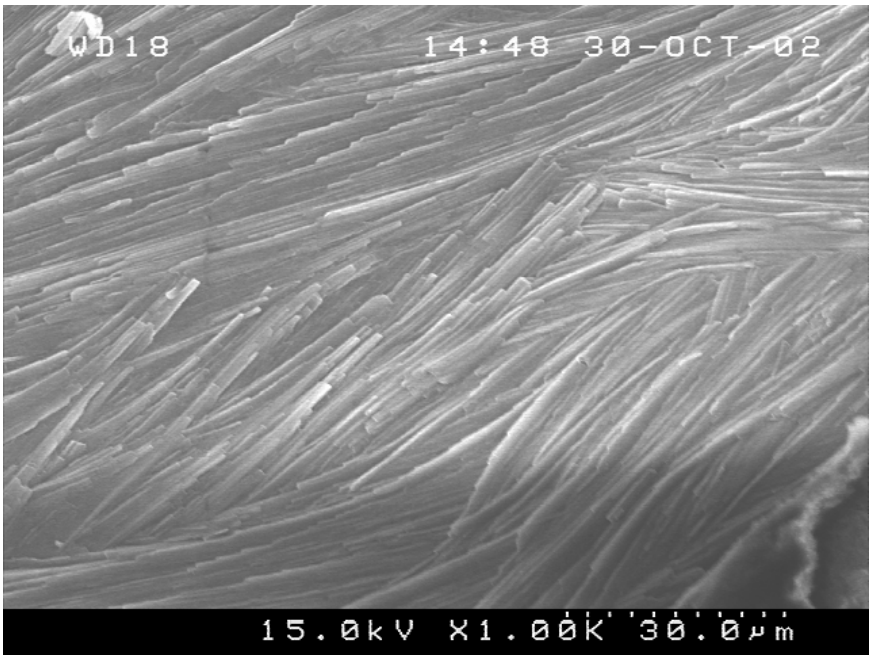

Figure 4.8: SEM micrographs of the surface of hot-melt extruded matrix tablets containing 30% guaifenesin and 70% “Coarse” ethyl cellulose processed at 90, 105, 105, 110°C viewed at 1,000 X magnification.

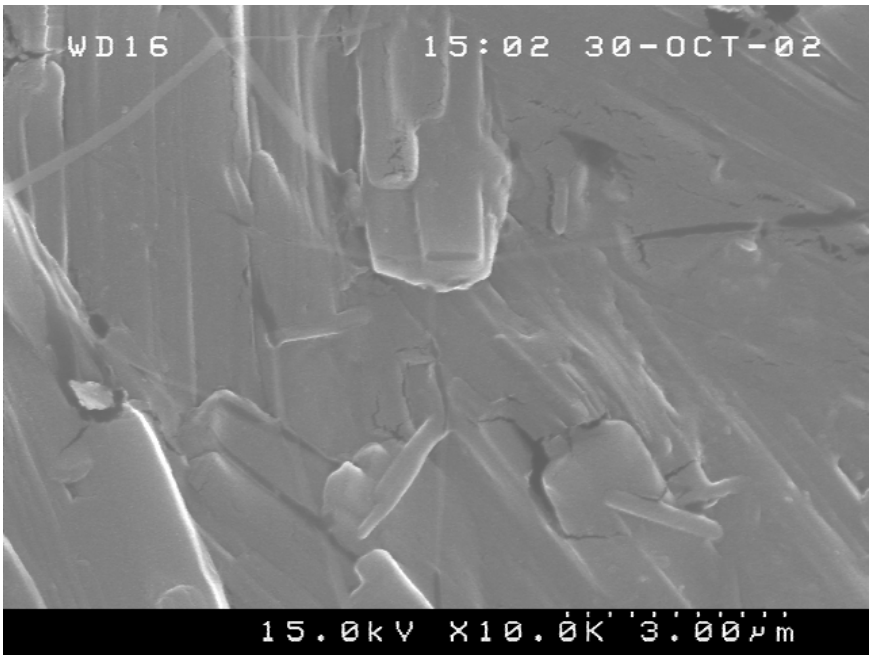

Figure 4.9: SEM micrographs of the surface of hot-melt extruded matrix tablets containing 30% guaifenesin and 70% “Coarse” ethyl cellulose processed at 90, 105, 105, 110°C viewed at 10,000 X magnification.

4.5.5 Pore Characteristics Prior to & After Dissolution Testing

The pore characteristics of the hot-melt extruded matrix tablets measured after dissolution testing are reported in Table 4.1. Tablets prepared by direct compression could not be analyzed due to matrix erosion and disintegration during dissolution testing. Statistically significant differences were observed in median pore radius ($n = 3$, $p < 0.01$), percent effective porosity ($n = 3$, $p < 0.0006$) and tortuosity ($n = 3$, $p < 0.00004$). Following dissolution testing, the median pore radius increased from 137 – 392 Å to 521 – 642 Å, the porosity increased from 0.4 – 2.3% to 7.8 – 8.7%, and the tortuosity decreased from 53.2 – 321 to 4.4 – 5.2. Prior to dissolution testing, the pores are primarily voids within the matrix. Following dissolution, the increase in median pore size and porosity is due to capillary diffusion of guaifenesin from the matrix. As guaifenesin particles on the outer surface of the tablet diffuse, a less tortuous pore network is created.

The surface morphology of the hot-melt extruded matrix tablets following a 24 hour dissolution test is presented in Figure 4.10 and 4.11. When viewed at 1,000 x magnification, the tablet surface was found to be smooth and no pores were visible. However, when viewed at 10,000 x

magnification, pores were clearly evident. The tablet surface after dissolution testing was smoother due to hydrodynamic shearing forces from the agitated dissolution medium and the greater number of pores is due to capillary diffusion of guaifenesin.

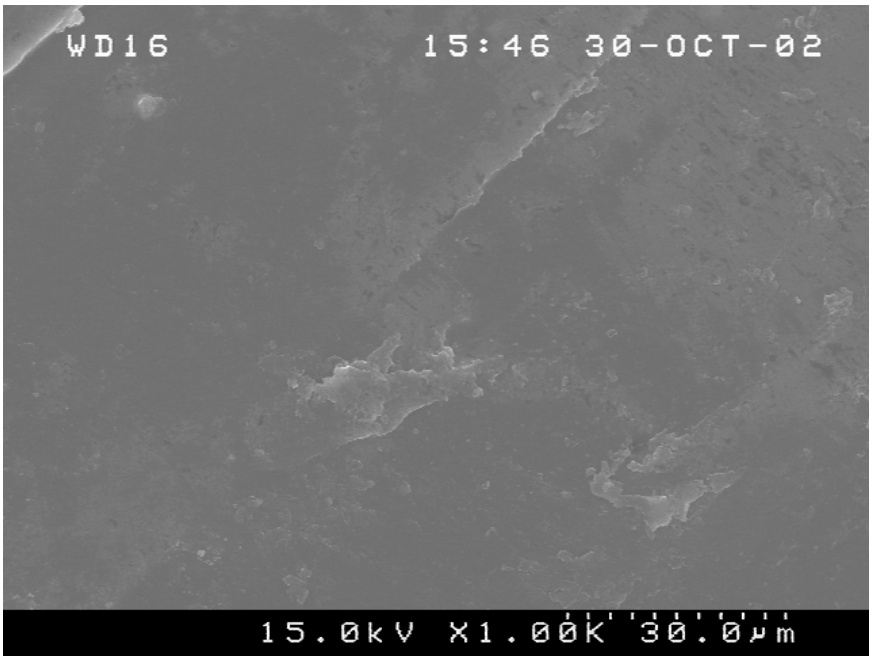

Figure 4.10: SEM micrographs at 1,000X magnification of the surface of hot-melt extruded matrix tablets containing 30% guaifenesin and 70% “Coarse” ethyl cellulose processed at 90, 105, 105, 110°C measured after 24 hour dissolution testing.

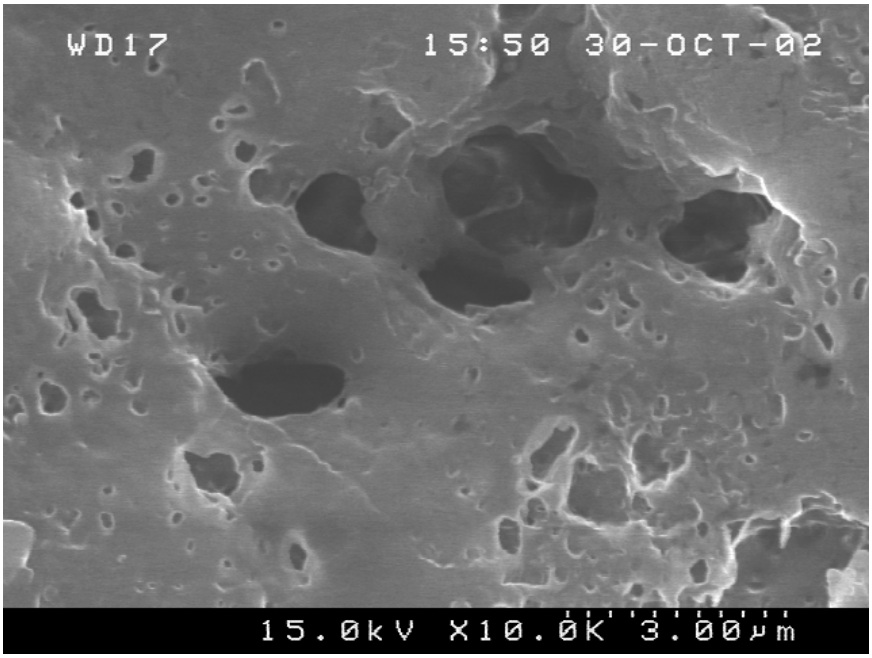

Figure 4.11: SEM micrographs at 10,000X magnification of the surface of hot-melt extruded matrix tablets containing 30% guaifenesin and 70% “Coarse” ethyl cellulose processed at 90, 105, 105, 110°C measured after 24 hour dissolution testing.

4.5.6 Determination of Drug Release Kinetics

The dissolution data were plotted according to the Higuchi equation (Figures 4.12 and 4.13) and the kinetic data are shown in Table 4.2. A higher deviation from the theoretical prediction was observed for matrix tablets prepared by direct compression using “coarse” ethyl cellulose at low compaction forces. The mechanism of release from these tablets was due to both diffusion and erosion. These tablets possessed very large pores and were considerably more porous and less tortuous than tablets prepared with “fine” ethyl cellulose. The tablets prepared by direct compression were completely eroded at the conclusion of the dissolution test, irrespective of the particle size of ethyl cellulose.

In contrast to directly compressed tablets, tablets prepared by hot-melt extrusion exhibited much slower drug release and a lag time was present. The hot-melt extruded tablets prepared by with “fine” ethyl cellulose demonstrated an initial lag time in drug release compared to those prepared with “coarse” ethyl cellulose. The lag time is indicated by the positive time intercept on the regression lines predicted by the Higuchi model. Lag times correspond to the time necessary for the dissolution medium to wet the tablet matrix and enter the pores. These tablets have

a lag time because they have a smaller pore size, are less porous and more tortuous.

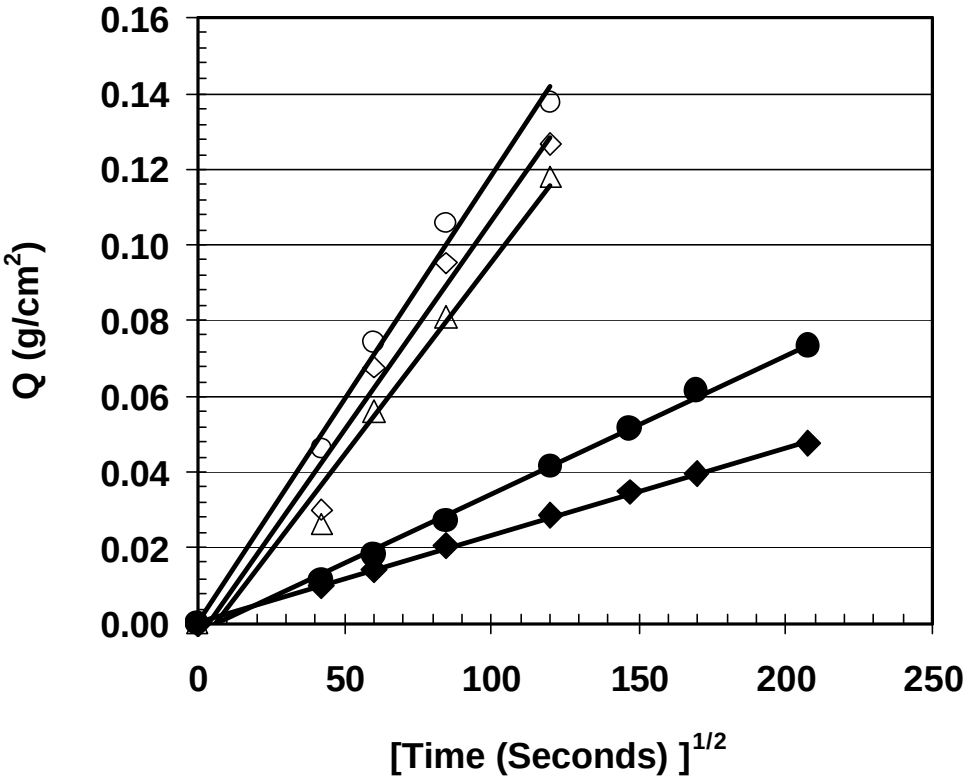

Figure 4.12: Higuchi Diffusion model fitting of the guaifenesin release data from matrix tablets prepared by direct compression and hot-melt extrusion.

Matrix tablets prepared using "Fine" ethyl cellulose (325 – 80 Mesh)

- o Direct Compression, 10 kN
- ◊ Direct Compression, 30 kN
- ∆ Direct Compression, 50 kN
- • Hot-Melt Extrusion, 80, 85, 85, 90°C
- ♦ Hot-Melt Extrusion, 90, 105, 105, 110°C

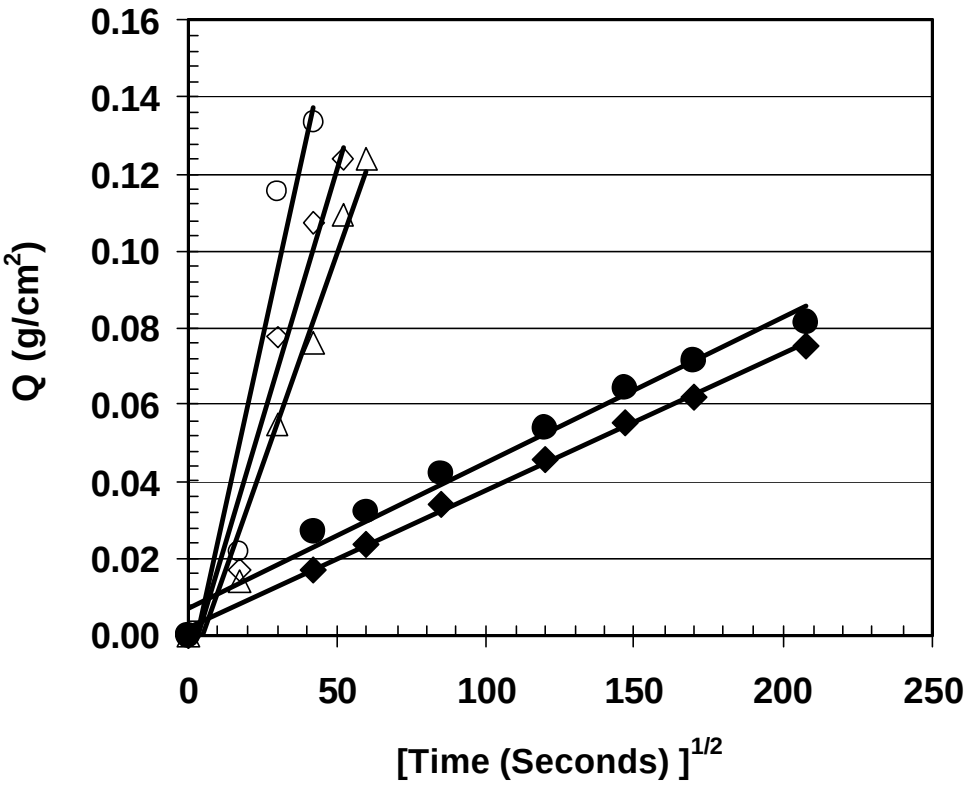

Figure 4.13: Higuchi Diffusion model fitting of the guaifenesin release data from matrix tablets prepared by direct compression and hot-melt extrusion.

Matrix tablets prepared using “Coarse” ethyl cellulose (80 – 30 Mesh)

- o Direct Compression, 10 kN
- ◊ Direct Compression, 30 kN
- ∆ Direct Compression, 50 kN
- • Hot-Melt Extrusion, 80, 85, 85, 90°C
- ♦ Hot-Melt Extrusion, 90, 105, 105, 110°C

Table 4.2: Kinetic data from regression fitting to Higuchi Diffusion Model giving the rate constant k ($g/cm^2s^{1/2}$), the y-intercept (g/cm^2), the correlation coefficient r^2, the apparent diffusion coefficient D_{app} (cm^2/s) and the diffusion coefficient D_s from the plot of drug release (g/cm^2) against the square root of time ($s^{1/2}$).

Processing Conditions	k ($g/cm^2s^{1/2}\times10^3$)	y-int. ($g/cm^2\times10^3$)	r^2	D_{app} ($cm^2/s\times10^6$)	D_s ($cm^2/s\times10^3$)
"Fine" Ethyl Cellulose (325 - 80 mesh)					
DC 10 kN	1.18	0.04	0.995	86.6	9.9
DC 30 kN	1.10	- 4.03	0.975	75.2	11.9
DC 50 kN	1.01	- 6.02	0.981	63.1	14.1
HME 80, 85, 85, 90°C	0.43	0.85	0.999	11.3	60.2
HME 90, 105, 105, 110°C	0.37	- 0.25	0.997	8.35	669.7
"Coarse" Ethyl Cellulose (80 - 30 mesh)					
DC 10 kN	3.08	- 4.68	0.899	598	12.0
DC 30 kN	2.48	- 6.32	0.961	386	14.2
DC 50 kN	2.19	- 10.4	0.971	300	16.2
HME 80, 85, 85, 90°C	0.38	7.21	0.980	8.90	16.2
HME 90, 105, 105, 110°C	0.36	1.69	0.998	7.91	141.3

4.6 CONCLUSIONS

The results of this study demonstrate that the guaifenesin release rate was dependent upon the particle size of ethyl cellulose and the processing conditions employed to prepare the tablets. The guaifenesin release rate was slower in tablets prepared with the “fine” ethyl cellulose particle size fraction due to the presence of fewer soluble drug clusters within the matrix. Tablets prepared by hot-melt extrusion exhibited considerably slower drug release relative to those prepared by direct compression. Thermal analysis demonstrated that guaifenesin was dispersed in ethyl cellulose at the molecular level in tablets prepared by hot-melt extrusion. The surface morphology of the hot-melt extruded tablets was found to depend upon processing temperature. The guaifenesin release rate also decreased with increasing compaction force in tablets prepared by direct compression due to greater densification of the powder bed. Analysis of the tablet pore characteristics could be correlated to the observed dissolution results. Drug release in hot-melt extruded tablets was found to be in good agreement with the Higuchi Diffusion model. Tablets prepared by direct compression using “coarse”

ethyl cellulose were found to release guaifenesin by both diffusion and erosion.

4.7 ACKNOWLEDGEMENTS

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CHAPTER 5 THE INFLUENCE OF GUAIFENESIN AND KETOPROFEN ON THE PROPERTIES OF HOT-MELT EXTRUDED POLYETHYLENE OXIDE FILMS

5.1 ABSTRACT

Films containing polyethylene oxide (PEO) and a model drug, either guaifenesin (GFN) or ketoprofen (KTP), were prepared by hot-melt extrusion. The thermal properties of the hot-melt extruded films were investigated using differential scanning calorimetry (DSC). Scanning electron microscopy (SEM) was used to examine the surface morphology of the films, and wide angle x-ray diffraction (XRD) was used to investigate the crystalline properties of the polymer, drugs and physical mixtures as well as the solid state structure of the films. The stability of the polymer was studied using gel permeation chromatography. The mechanical properties, including percent elongation and tensile strength of the films were determined on an Instron according to ASTM procedures. The Hoftyzer / van Krevelen method for calculation of the Hansen solubility parameter was calculated to estimate the likelihood of drug-polymer miscibility. Both GFN and KTP were stable during the

extrusion process. XRD suggested that GFN crystallized from the melt upon cooling, but KTP formed a solid solution. Melting points corresponding to the crystalline drugs were not observed in the films by DSC analysis. Crystallization of GFN on the surface of the film could be observed using SEM at all concentrations studied, but KTP crystallization did not occur until reaching the 15% level. GFN and KTP were found to decrease drive load, increase PEO stability and plasticize PEO the polymer during extrusion. The Hansen solubility parameters calculated using the Hoftyzer / van Krevelen method predicted miscibility between PEO and KTP and poor miscibility between PEO and GFN. The predictions of the solubility parameters were in agreement with the XRD and SEM results. The percent elongation decreased with increasing GFN concentrations, but significantly increased with increasing KTP concentrations. Both GFN and KTP decreased the tensile strength of the extruded film.

5.2 INTRODUCTION

The transdermal and transmucosal route of drug administration offers many advantages to other methods of drug delivery, especially when the drug undergoes either a substantial first pass effect or local

therapy is desired. Polymeric films are used to deliver drugs in transdermal and transmucosal systems and may function as backing materials, drug reservoirs, micro-porous or semi-permeable membranes and bioadhesive layers. Transdermal and transmucosal films for drug delivery are generally produced by casting from organic or aqueous solvent systems. In addition to long processing times, high cost and environmental concerns, several researchers have reported that cast films are not mechanically stable [10, 87, 89, 155-157]. The instability of cast films has been attributed to polymer chain relaxation, moisture absorption and polymer-plasticizer interaction during storage.

Hot-melt extrusion has received considerable attention in the pharmaceutical industry. Several research groups have demonstrated the hot-melt extrusion technique to be a viable method to prepare pharmaceutical dosage forms including granules [2], pellets [4, 158], sustained release tablets [5-7] and topical and transdermal drug delivery systems [10-17]. A number of studies have recently shown the potential of hot-melt extrusion techniques to form solid solutions and solid dispersions [5, 30, 76, 91, 159].

The formation of a solid dispersion has been found to influence the properties of the dosage form. Aitken-Nichol and coworkers found that

hot-melt extrusion was a viable method to produce thin, flexible films for topical drug delivery using Eudragit E100 [10]. Hot-melt extruded films were compared to cast films and differences were observed in the dissolution rate and mechanical properties. These researchers reported that lidocaine hydrochloride was able to plasticize the hot-melt extruded film. The authors concluded that the differences in dissolution rate and mechanical properties were due to dissolution of the drug in polymer when prepared by hot-melt extrusion.

Polyethylene oxide has been widely used in a variety of dosage forms [5, 93, 94, 96, 97], including transdermal and transmucosal dosage forms [11, 95, 160-163]. PEO is semi-crystalline, bioadhesive and mucoadhesive due to its water solubility, hydrophilicity, high viscosity, ability to form hydrogen bonds and biocompatibility [164]. PEO has been previously studied for the production of hot-melt extruded tablets [5, 7] and as an adjuvant in hot-melt extruded hydroxypropylcellulose films [13].

Despite its wide usage, few studies have been reported in the scientific literature on the properties of PEO films as a drug reservoir and bioadhesive layer for transdermal drug delivery. Furthermore, there are no reports in the literature on the influence of drugs on the properties of hot-melt extruded polyethylene oxide films. Therefore, the objectives of

this study were to investigate the physicochemical and mechanical properties of hot-melt extruded PEO films containing either guaifenesin or ketoprofen as model drugs. Guaifenesin and ketoprofen were used as model drugs used in this study. Both compounds are crystalline with poor water solubility.

5.3 MATERIALS AND METHODS

5.3.1 Materials

Guaifenesin and ketoprofen were purchased from Spectrum Laboratory Products (Gardena, CA). Polyethylene Oxide (Polyox WSR-N80, molecular weight 200,000) was kindly donated by the Dow Chemical Company (Midland, MI). HPLC solvents were purchased from EM Science (Gibbstown, NJ).

5.3.2 Methods

5.3.2.1 Hot-Melt Extrusion

Model formulations containing the polymer and 0, 5, 10, 15 and 30% (w/w) of either drug were prepared by geometric dilution, then introduced into a V Blender (Blend Master®,Patterson-Kelley, East

Stroudsburg, PA) and mixed for 15 minutes. The powder blend (250 grams) was fed into a single-screw Randcastle Extruder (Model RC 0750, Cedar Grove, NJ) equipped with a Nitralloy 135M screw (3:1 compression ratio with flight configuration containing feed, compression and mixing sections) and a 6 inch flex film die. The screw speed was 40 rpm. The three heating zones and die temperature were set to 60, 75, 90 and 100°C and allowed to equilibrate. The residence time of the materials in the extruder was approximately 2 – 3 minutes. The films were wound and collected in rolls. The film thickness ranged from 0.30 to 0.45 mm and the width was 10 cm.

5.3.2.2 Drug Content

The film samples were analyzed for guaifenesin content using a Waters (Milford, MA) high performance liquid chromatography (HPLC) system with a photodiode array detector (Model 996) extracting at 276 nm. The mobile phase was a mixture of water:methanol:glacial acetic acid in volume ratios of 600:400:15. The solvents were vacuum filtered through a 0.45 μm nylon membrane and degassed by sonication. Samples were dissolved in mobile phase and pre-filtered through a 0.45 μm membrane (Gelman Laboratory, GHP Acrodisc). An auto sampler

(Model 717plus) was used to inject 20μL samples. The data were collected and integrated using Empower® Version 5.0 software. The column was an Alltech Alltima™ C_{18} 3 μm, 150 × 4.6 mm. The flow rate was 1.0 ml/min. The retention time of the guaifenesin was 4 minutes. Linearity was demonstrated from 2 to 200 μg/ml (R^2 = 0.997) and injection repeatability was 0.35% relative standard deviation for 10 injections.

Samples were analyzed for ketoprofen using HPLC extracting at 256 nm. The column was an Alltech Alltima™ C_{18} 3 μm, 150 × 4.6 mm and the mobile phase was 55% acetonitrile, 45% 20mM pH 4 acetate buffer. The flow rate was 1 ml/min and the ketoprofen retention time was 5.2 minutes. Linearity was demonstrated from 1 to 200 μg/ml (R^2 = 0.995) and injection repeatability was 0.62% relative standard deviation for 10 injections.

5.3.2.3 Wide Angle X-Ray Diffraction

The crystalline properties of the film samples were examined by wide angle X-ray diffraction. Film samples measuring 20 × 15 mm were introduced to a Philips 1710 X-ray diffractometer with a CuKα target, diffracted beam monochromatic filter and variable divergent slit (Philips

Electronic Instruments, Inc., Mahwah, NJ) using Jade 5 XRD pattern processing software (Materials Data, Inc., Irvine, CA). The voltage was set to 40 kV and the current was set to 40 mA. Samples were analyzed in the 2-Theta range from 5-55° using a 0.05° step size with a 1-second dwell time at each step.

5.3.2.4 Differential Scanning Calorimetry

Differential Scanning Calorimetry (DSC) was used to characterize the thermal properties of the polymer, drug, physical mixtures and hot-melt extruded films. The DSC instrument was a model 2920 from TA Instruments (New Castle, DE) running in standard mode and equipped with Universal Analysis 2000 software. Ultrahigh purity nitrogen was used as the purge gas at a flow rate of 150 ml/min. The sample was weighed to 10 ± 5 mg and placed in aluminum pans (Kit 0219-0041, Perkin-Elmer Instruments, Norwalk, CT) and crimped with an aluminum lid. The temperature ramp speed was 10°C per minute from 25°C to 115°C for all studies.

5.3.2.5 Scanning Electron Microscopy

Scanning electron microscopy was used to study the surface morphology of the hot-melt extruded films. The samples were mounted

on an aluminum stage using adhesive carbon tape and placed in a low humidity chamber for 12 hours prior to analysis. Samples were coated with gold-palladium for 60 seconds under an argon atmosphere using a Pelco® Model 3 Sputter Coater (Ted Pella, Inc., Redding, CA) in a high vacuum evaporator equipped with an omni-rotary stage tray. Scanning electron microscopy was performed using a Hitachi S-4500 field emission microscope operating at an accelerating voltage of 10 kV and a 15 μA emission current. Images were captured with Quartz® PCI software (Quartz Imaging Corporation, Vancouver, B.C. Canada).

5.3.2.6 Gel Permeation Chromatography

The weight average molecular weight of PEO was determined as previously reported [7]. Briefly, the mobile phase was double-distilled water containing 0.1 M sodium nitrate. All standards and samples were prepared at 0.5% w/w concentrations in mobile phase under gentle agitation on a radial shaker (Aberbach Corp, Ann Arbor, MI) for 12 hours and injected immediately. A Waters analytical system used for analysis included a WISP model 710B auto sampler (100μl sample injection volume), model 510 pump, Ultrahydrogel® Columns (2000 and 1000 in series) and a model 410 differential refractometer as the detector. The

data were collected using Empower® Version 5.0 software. A third order calibration curve (R^2 = 0.99) was constructed using PEO standards (Polymer Standards Service, Silver Spring, MD) with peak molecular weights ranging from 4,450 to 1,700,000. The flow rate was 0.8 ml/min and the columns were held at an operating temperature of 35°C during analysis. Injection precision was found to have a relative standard deviation of 1.3% for 10 injections.

5.3.2.7 Mechanical Testing

The stress and strain mechanical properties of the films were determined utilizing an Instron 4201 testing apparatus operating in accordance with the standard test method for tensile properties of thin plastic sheeting by the American Society for Testing Materials, method D882-02 [165]. The film samples were stored for 12 hours prior to testing to equilibrate at 25°C and 60% relative humidity. Six samples from each film formulation were cut in the direction of machine flow into rectangles (150 mm long by 10 mm wide). Twenty five millimeters of tape was applied to each end to prevent grip rupture. The Instron was set with a full scale load of 50 N and a cross head speed of 25 mm/min. The initial grip separation was 100 mm. The thickness of each rectangle was

measured along the centerline in 10 places and recorded. Testing conditions for all films were 25°C and 60% relative humidity. The samples were extended until they ruptured and the load, stress, strain and peak load were calculated.

5.3.2.7 Statistical Analysis

One-way analysis of variance (ANOVA) was used to determine statistically significant differences between results. Results with p-values < 0.05 were considered statistically significant.

5.4 Results & Discussion

5.4.1 Physicochemical Characterization of Hot-melt Extruded PEO Films and Films containing Guaifenesin and Ketoprofen

The hot-melt extruded PEO film and the hot-melt extruded films containing guaifenesin and ketoprofen were clear, homogenous and flexible. Both GFN and KTP were found to be stable during hot-melt extrusion. The drug content was assayed using HPLC. Excellent agreement was found between the formulated content and the values

determined after thermal processing (≥99%). There was no change in the peak retention time and no additional peaks were observed.

PEO is a semi-crystalline polymer, and GFN and KTP are crystalline drugs. The X-ray diffraction (XRD) patterns of PEO, GFN, KTP, physical mixtures and the hot-melt extruded films are presented in Figures 5.1 and 5.2. The highest crystalline PEO peak occurred at a 2θ angle of 23.5 and a smaller, distinct peak was also observed at 19.1 2θ angles. GFN has distinct crystalline peaks at 12.1, 13.6 and 20.8 2θ angles and a series of smaller peaks at 22.55, 23.80, 25.50, 27.5 2θ angles.

The PEO crystalline peaks at 19.1 and 23.5° 2θ° were observed in the drug free hot-melt extruded film, but were broad and less intense than the powder sample. The reduction in peak intensity was associated with a decrease in crystallinity and the peaks became more broad due to a wider distribution of crystal sizes. The diffraction patterns of the physical mixtures composed of PEO and GFN exhibit crystalline peaks corresponding to PEO (19.1, 23.5 2θ°), but the XRD technique was not able to detect GFN peaks until the GFN concentration reached the 10% level. PEO and GFN crystalline peaks were also present in the hot-melt extruded films at the higher GFN levels. At GFN loads of 10, 15 and 30%,

the GFN peaks at 12.1°, 13.6° and 20.8° were more intense in the hot-melt extruded films than in the physical mixtures. The increase in peak intensity following thermal treatment suggests that two distinct phases formed upon cooling. The XRD technique is sensitive to crystal orientation. After hot-melt extrusion, the increase in peak intensity is likely due to a preferential orientation of crystals within the film.

The largest crystalline peak in KTP can be observed at a 2θ angle of 22.85 with smaller peaks at 6.4, 14.4 and 18.4 2θ angles (Figure 5.2). The diffraction patterns of the physical mixtures composed of PEO and KTP also exhibit PEO crystalline peaks (19.1, 23.5 2θ angles). However, XRD was not able to detect KTP peaks until the KTP concentration in the film reached 10%. In contrast to the GFN film, the diffraction pattern of the hot-melt extruded KTP film showed peaks corresponding to PEO, but peaks associated with KTP were absent. This finding suggests that KTP was fully dissolved in the polymer following extrusion.

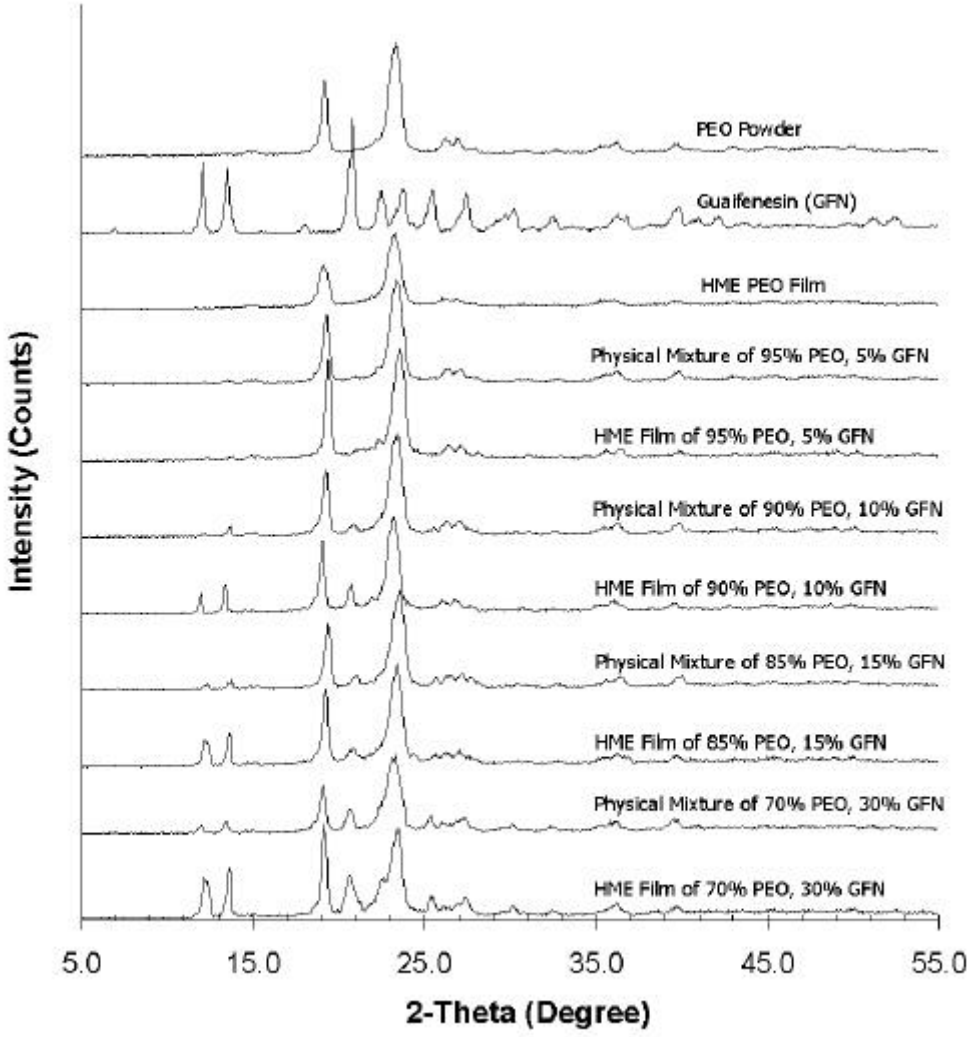

Figure 5.1: Wide angle X-Ray diffraction profiles of PEO powder, guaifenesin, hot-melt extruded PEO film, physical mixtures of PEO and guaifenesin and hot-melt extruded films of PEO and guaifenesin.

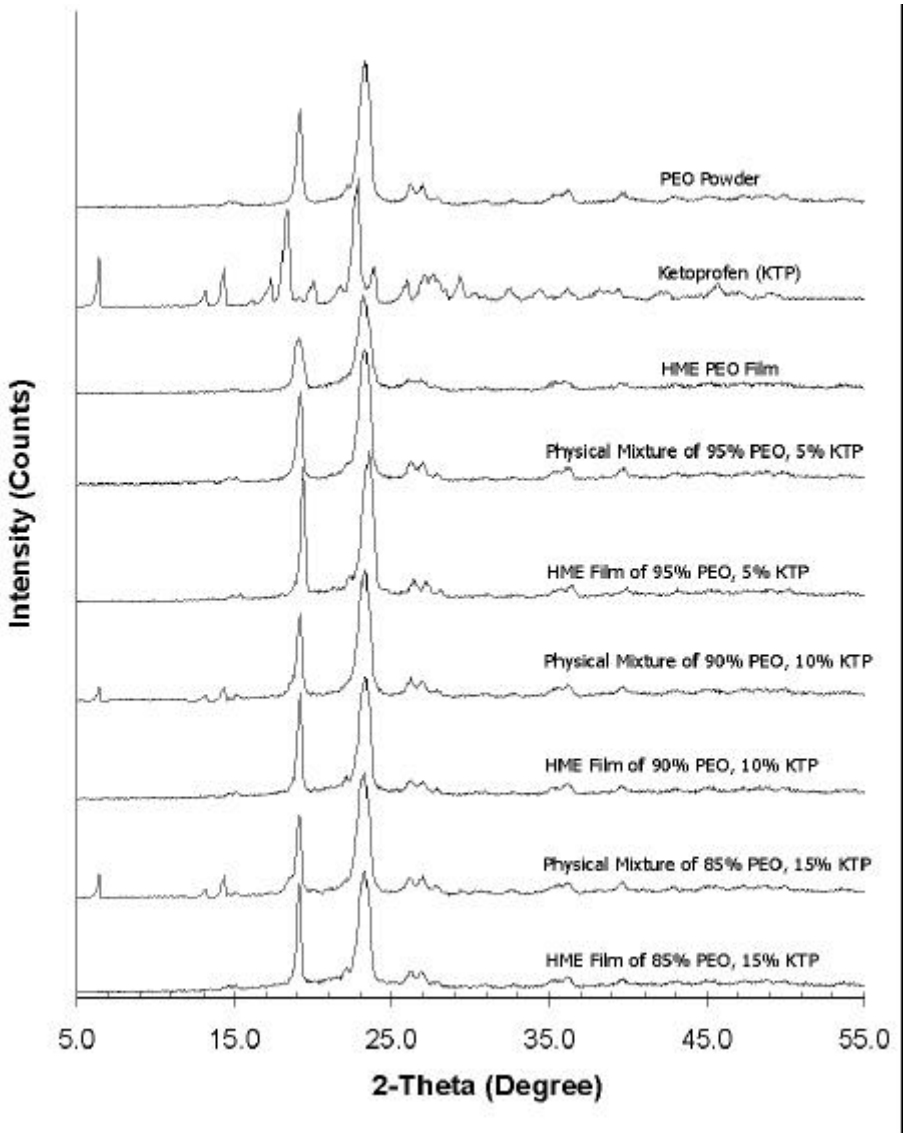

Figure 5.2: Wide angle X-Ray diffraction profiles of PEO powder, ketoprofen, hot-melt extruded PEO film, physical mixtures of PEO and ketoprofen and hot-melt extruded films of PEO and ketoprofen.

The thermal properties of the polymer, drugs, physical mixtures and films were investigated using DSC. GFN in its crystalline form produced an endotherm representing its melting point at 85.6°C (Figure 5.3). The PEO melting point can be observed at 68.9°C. The physical mixture of PEO and GFN exhibits a broad peak at 67.6°C. This thermal transition was more broad than the individual pure materials and suggests that melting of PEO and solubilization of GFN occurred simultaneously. A thermal transition associated with a GFN melting point is not evident in the physical mixture or the drug loaded films. Indeed, these findings contradict the presence of GFN crystallinity determined by XRD. It can be reasoned that GFN and PEO were miscible in the molten state at elevated temperatures, but GFN crystallized into a separate phase upon cooling. The GFN recrystallization process could not be captured on the DSC time scale. The presence of GFN crystals in the films is reinforced by the significant depression of the PEO melting point. Pure materials generally exhibit sharp melting points. The introduction of an impurity into a crystalline material causes a broadening of the melting range and often, a depression in the melting point. As the GFN concentration in the film increased, the thermogram exhibited a depression and broadening of the

PEO melting point. The reduction and broadening of the melting transition also suggests the presence of smaller crystals and a wider distribution of crystal sizes.

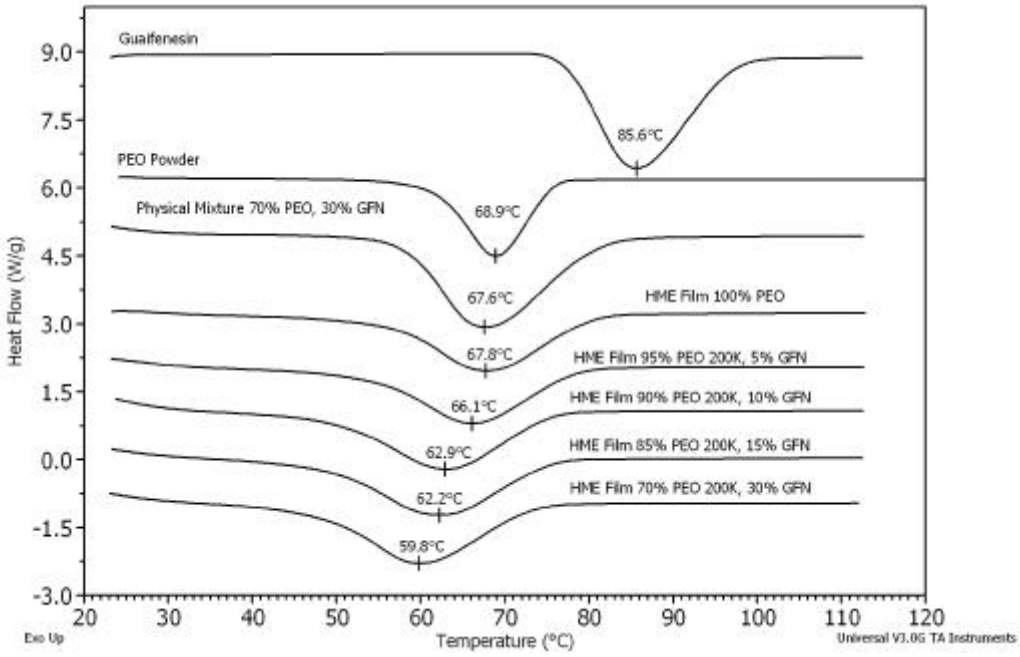

Figure 5.3: Differential Scanning Calorimetry profiles of PEO, guaifenesin, a physical mixture of GFN and PEO, and GFN loaded films.

Ketoprofen loaded films were also studied by DSC (Figure 5.4). KTP in its crystalline form produced an endotherm at 96.2°C corresponding to the melting point. Physical mixtures and hot-melt extruded films of PEO and KTP show a broad peak at 65°C corresponding to PEO, but do not exhibit an endotherm corresponding to KTP. Similar to the GFN films, as the KTP concentration in the film increased, the endotherm representing the PEO melting point was depressed to a greater extent and became broader. These results support the conclusions from the XRD data that KTP dissolved in the molten PEO during extrusion and did not recrystallize upon cooling.

Scanning electron microscopy was used to examine the surface morphology of films (Figures 5.5 – 5.12). The drug free PEO film has a clear and homogenous surface with few visible crystals (Figure 5.5). However, the micrograph of the GFN loaded films revealed that crystal formation had occurred. Surface crystallization increased with increasing GFN concentrations (Figure 5.6 – 5.9). Furthermore, crystal orientation on the surface can be observed. In contrast, crystallization on the surface of the KTP loaded films was not observed until reaching the 15% level (Figure 5.10 – 5.12).

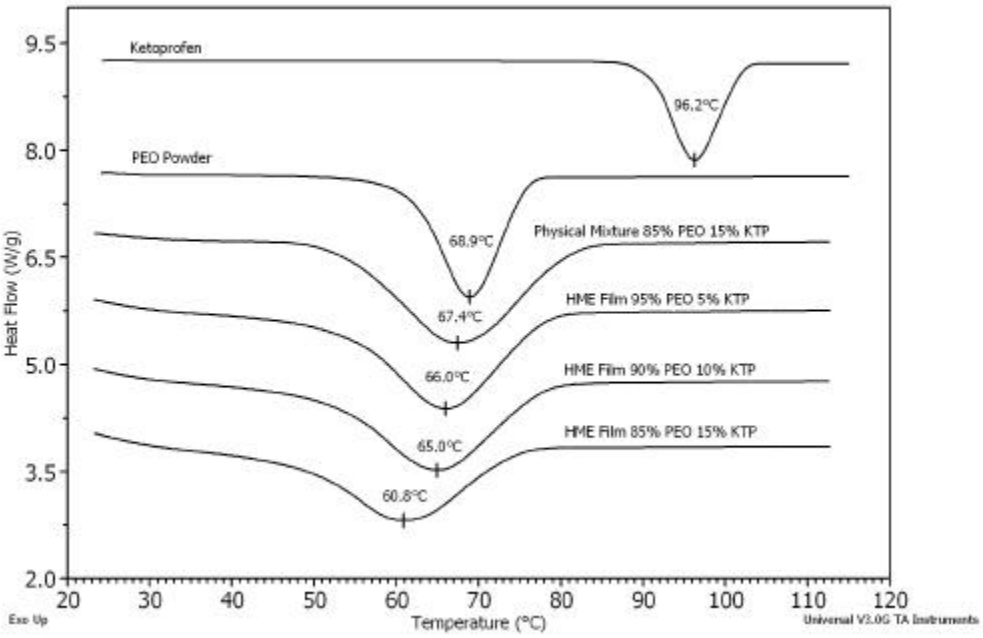

Figure 5.4: Differential Scanning Calorimetry profiles of PEO, ketoprofen, a physical mixture of KTP and PEO, and KTP loaded films.

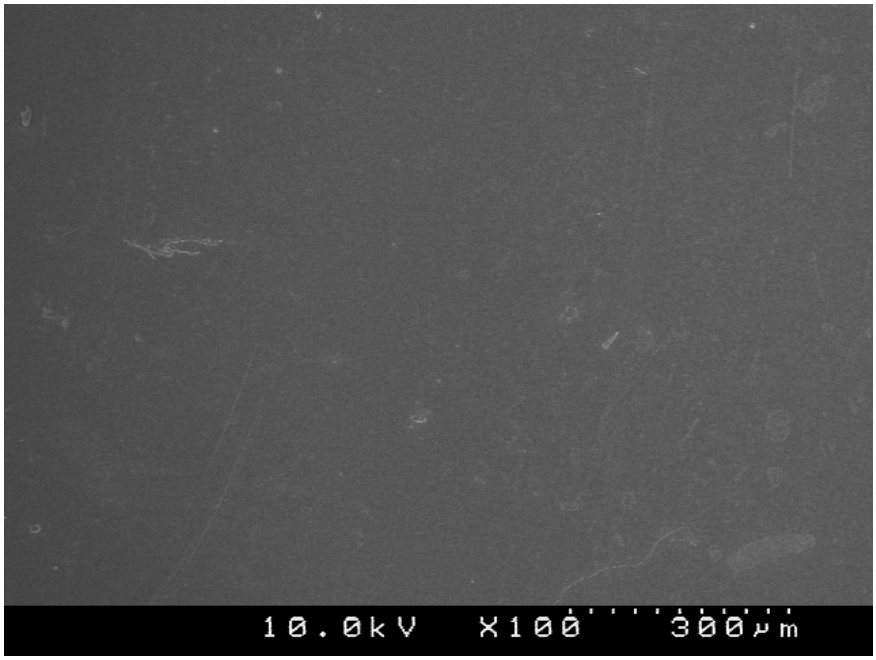

Figure 5.5: SEM micrograph of the surface morphology of hot-melt extruded PEO film at 100 x magnification.

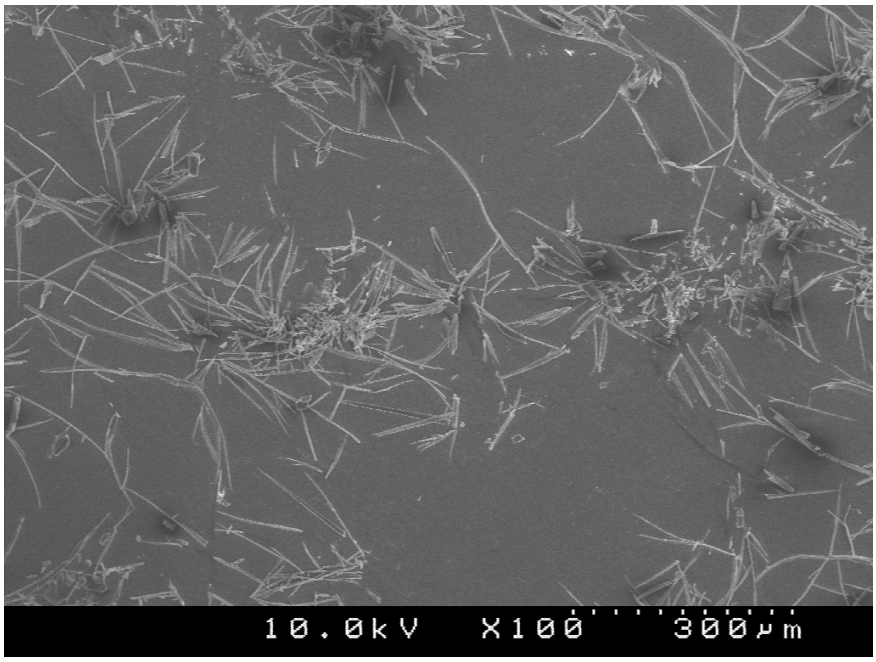

Figure 5.6: SEM micrograph of the surface morphology of hot-melt extruded film containing 95% PEO and 5% GFN at 100 x magnification.

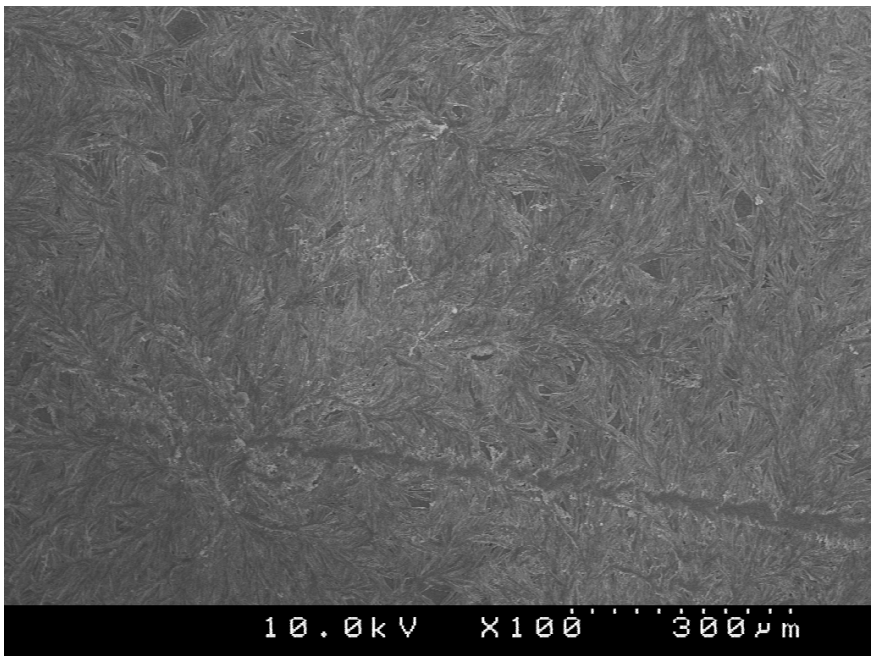

Figure 5.7: SEM micrograph of the surface morphology of hot-melt extruded film containing 90% PEO and 10% GFN at 100 x magnification.

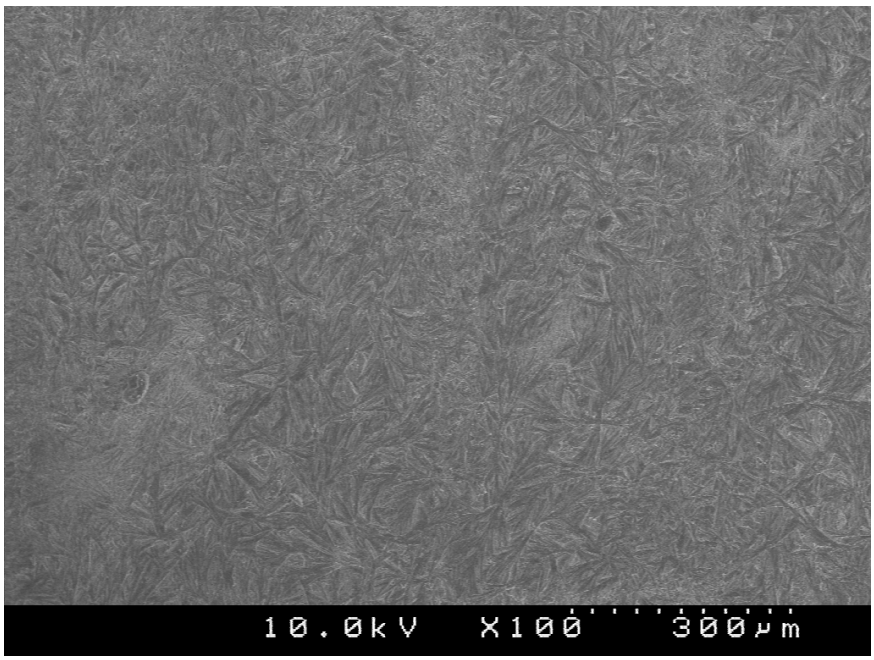

Figure 5.8: SEM micrograph of the surface morphology of hot-melt extruded film containing 85% PEO and 15% GFN at 100 x magnification.

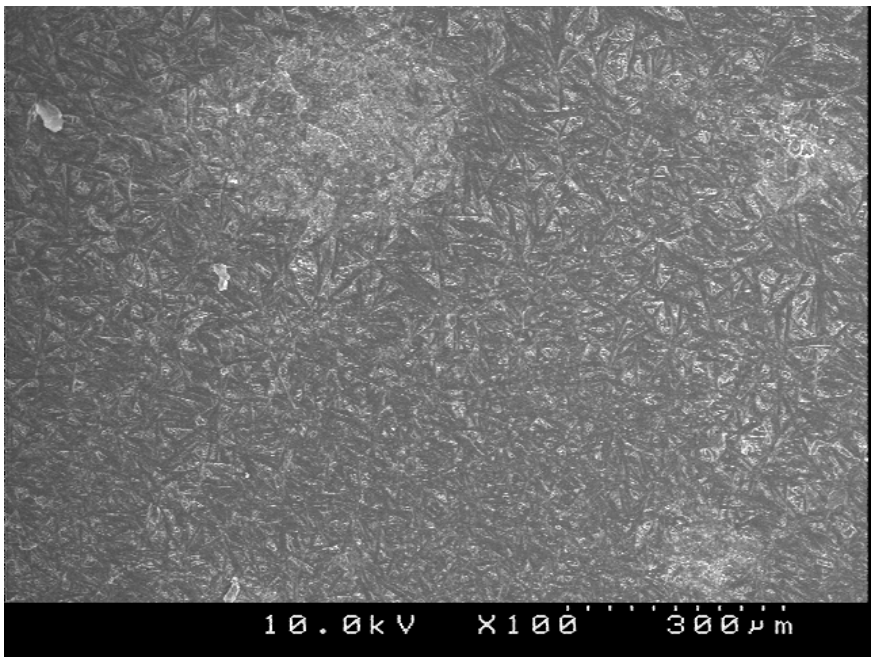

Figure 5.9: SEM micrograph of the surface morphology of hot-melt extruded film containing 70% PEO and 30% GFN at 100 x magnification.

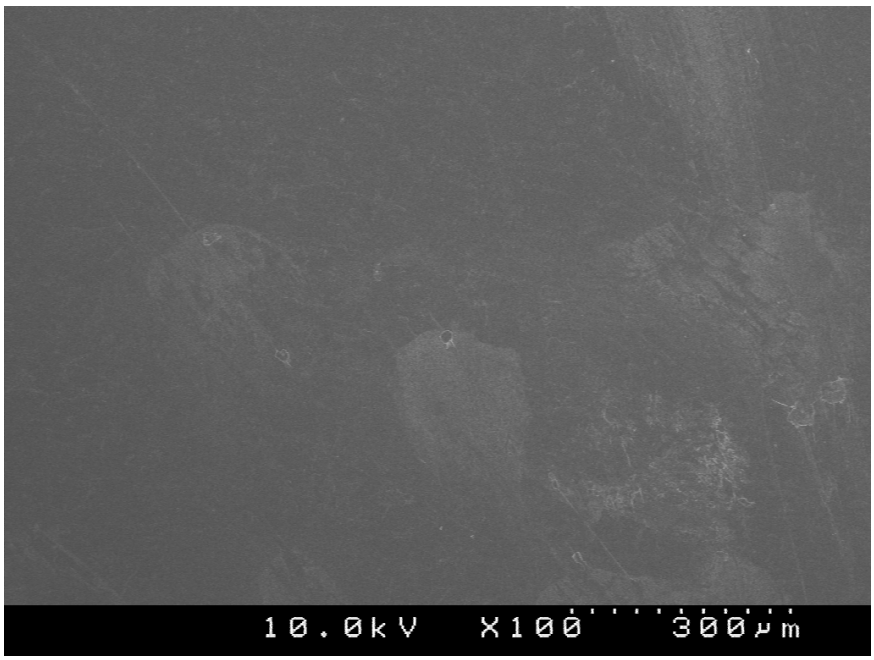

Figure 5.10: SEM micrograph of the surface morphology of hot-melt extruded film containing 95% PEO and 5% KTP at 100 x magnification.

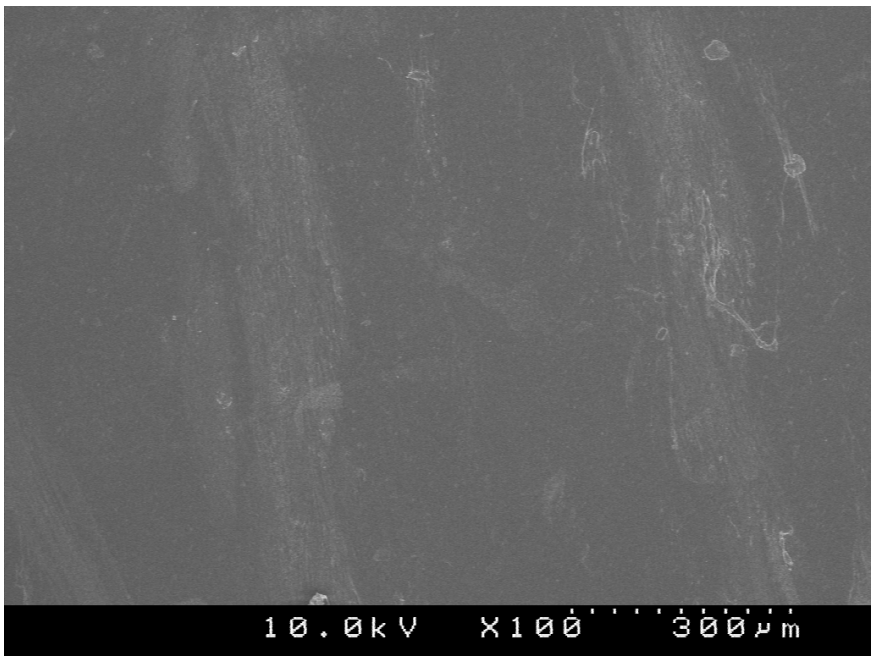

Figure 5.11: SEM micrograph of the surface morphology of hot-melt extruded film containing 90% PEO and 10% KTP at 100 x magnification.

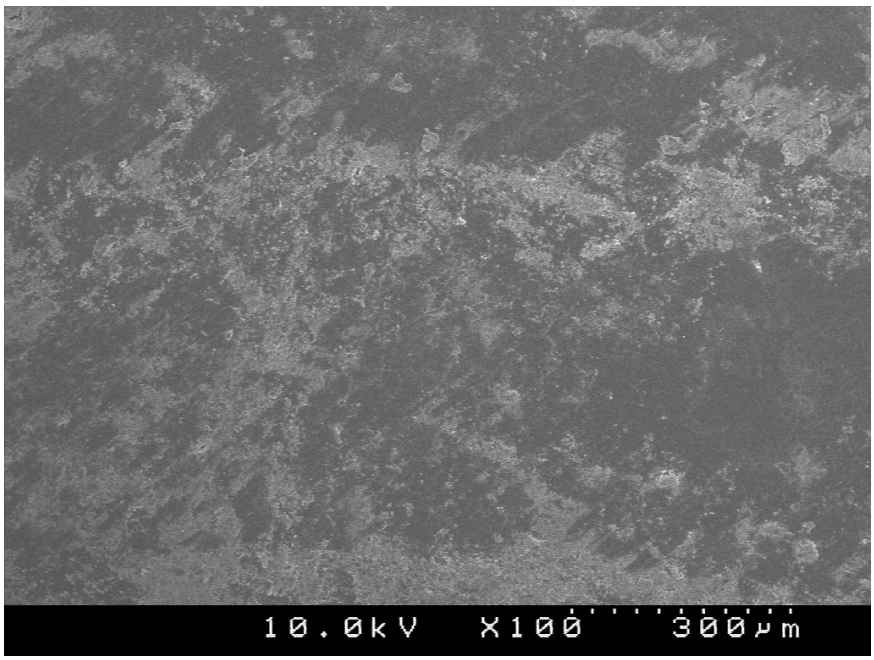

Figure 5.12: SEM micrograph of the surface morphology of hot-melt extruded film containing 85% PEO and 15% KTP at 100 x magnification.

Polymers are subject to mechanical, thermal and oxidative degradation during hot-melt extrusion. We have previously reported the stability of high molecular weight PEO in matrix tablets prepared by hot-melt extrusion [7]. Similarly, gel permeation chromatography was used in the present study to determine the molecular weight of PEO before and after hot-melt extrusion (Table 5.1). The weight average molecular weight of PEO decreased 6.8% after thermal processing when processed without GFN or KTP. GFN and KTP were found to reduce PEO molecular weight loss and to decrease the load on the extruder motor. A decrease in drive load suggests a reduction in melt viscosity (shear thinning), degradation (formation of lower molecular weight polymer chains) and or an improvement in polymer chain mobility. As the GFN and KTP concentration increased in the film, the drive amperage decreased and the stability of PEO increased. At higher drug concentrations, no change in molecular weight of the polymer was observed following the hot-melt extrusion process. These results suggest that GFN and KTP plasticize PEO during extrusion.

Table 5.1: Stability of PEO in Hot- Melt Extruded Films containing either Guaifenesin or Ketoprofen as Determined by Gel Permeation Chromatography**.**

Formulation			After Extrusion $M_w \times 10^3$	% Change	Drive Current (A)
PEO	GFN	KTP			
100			176 ± 14	- 6.8	2.2 – 2.4
95	5		180 ± 12	- 4.8	1.9 – 2.3
90	10		183 ± 11	- 3.2	1.6 – 1.8
85	15		190 ± 12	+ 0.5	1.4 – 1.6
70	30		191 ± 14	+ 1.1	1.4 – 1.6
95		5	184 ± 8	- 2.6	1.5 – 1.8
90		10	186 ± 11	- 1.6	1.1 – 1.6
85		15	188 ± 13	- 0.5	0.7 – 1.0

Unextruded PEO Mw 189 ± 9

Zone Temperatures: 50, 60, 70 and 80°C

Screw Speed: 40 rpm

Molecular weights are reported as mean ± standard deviation, n = 6.

5.4.2 Calculated Solubility Parameters of Guaifenesin, Ketoprofen and Polyethylene Oxide and their Relationship to the Experimental Results.

Solubility parameters (δ) have been used successfully to predict the miscibility of drugs with excipients and polymers in solid dispersions [38, 166-168]. Greenhalgh et al. suggested that interactions between polar (δ_p) and hydrogen bonding groups (δ_h) significantly affect solubility and should be incorporated into the estimation of Hildebrand solubility parameters, which account for dispersive forces (δ_d) only. The method of Hoftyzer and van Krevelen [169] can be used to estimate the Hansen solubility parameter with the incorporated values (δ_t) as described below:

$$d_t = \sqrt{d_d^2 + d_p^2 + d_h^2} \qquad \text{(Equation 5.1)}$$

Compounds with similar values for δ are likely to be miscible because the energy of mixing from intramolecular interactions is balanced with the energy of mixing from intermolecular interactions. The difference between the solubility parameters ($\Delta\delta$) of two materials gives an estimation of the likelihood that they will be miscible. Greenhalgh et. al.

demonstrated that compounds with $\Delta\delta_t$ < 7 $Mpa^{1/2}$ were likely to be miscible and compounds with $\Delta\delta_t$ > 10 $Mpa^{1/2}$ were likely to be immiscible.

Table 5.2 shows the interaction parameters and calculated solubility parameters for guaifenesin, ketoprofen and polyethylene oxide. The difference between the calculated solubility parameters of the polymer and the drugs predict that PEO and KTP are likely to be miscible, but that PEO and GFN are likely to be immiscible. Thus, the Hansen solubility parameter calculated using the method of Hoftyzer and van Krevelen supports the results of the XRD and SEM studies.

Table 5.2: Calculated Interaction Parameters and Solubility Parameters for Guaifenesin, Ketoprofen and Polyethylene Oxide.

	δ_d	δ_p	δ_h	δ_t ($Mpa^{1/2}$)
Guaifenesin	20.3	.31	18.4	27.5
Ketoprofen	18.7	.18	7.5	20.2
Polyethylene Oxide	17.8	.56	9.1	20.0
$\Delta\delta_t$ (GFN – PEO) = 7.5			$\Delta\delta_t$ (KTP – PEO) = 0.2	

δ_d is the dispersion forces parameter, δ_p is the polar interaction parameter, δ_h is the hydrogen bonding parameter and δ_t is the total solubility parameter calculated according to equation 5.1.

5.4.3 The Influence of Guaifenesin and Ketoprofen on the Mechanical Properties of Hot-melt Extruded Polyethylene Oxide Films

The tensile strength and percent elongation of the drug free and drug loaded PEO films are presented in Figures 5.13 and 5.14. The drug free PEO film was found to have a tensile strength of 12.8 ± 0.4 MPa and its percent elongation was 21.5 ± 3.1 %. Semi-crystalline polymers contain lamellar regions of folded chains which are held together by "tie molecules" which extend from one crystalline region to the next [170]. The crystalline regions are typically denser and harder than the amorphous regions. Chain ends and imperfections tend to occur in the amorphous regions between crystalline lamellae where few tie molecules exist. Thus, the tie molecules are the source of strength. Secondary intermolecular forces between polymer chains are also a source of strength. The degree of hydrogen bonding, van der Waals forces and dipole-dipole bonds depends upon the packing, flexibility and orientation of the polymer chains.

Semi-crystalline polymers tend to be brittle with little strength. The brittleness is thought to be due to strains imposed on the amorphous phase by the crystallites, voids introduced during crystallization or from

stress concentrations of crystallites [171]. Fractures generally occur in the boundaries between spherulites where few tie molecules exist or along the radii of large spherulites [171]. Thus, the mechanical properties of semi-crystalline polymers are largely determined by flaws and microscopic fractures.

The influence of guaifenesin and ketoprofen on the mechanical properties of hot-melt extruded PEO films is presented in Figures 5.13 & 5.14. The percentage elongation of the GFN loaded films was significantly less than the drug free film. As the guaifenesin concentration in the film increased from 5 to 30%, the elongation decreased from 25.1 to 41.4%, respectively, relative to the drug free PEO film. The tensile strength was reduced at all GFN concentrations studied compared to the drug free PEO film. An inverse relationship between tensile strength and guaifenesin concentration was observed. The tensile strength decreased as the guaifenesin concentration in the film increased to 15%. Statistically similar tensile strength values were obtained for films containing 15% and 30% guaifenesin.

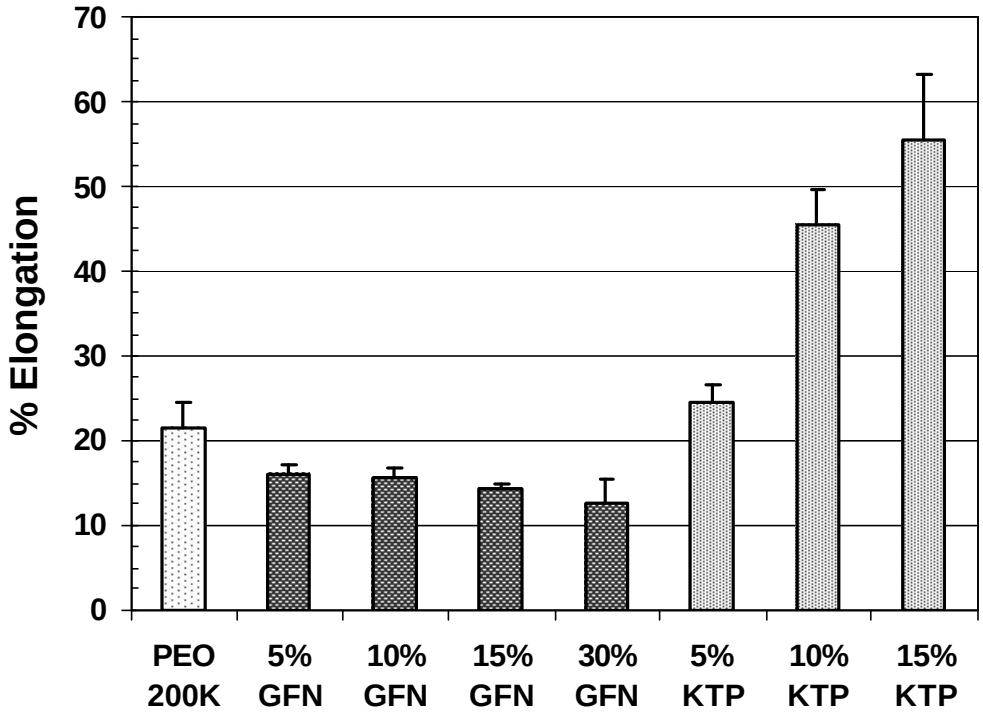

Figure 5.13: The percent elongation of hot-melt extruded polyethylene oxide (PEO) films and films containing various concentrations of guaifenesin (GFN) or ketoprofen (KTP), n= 6.

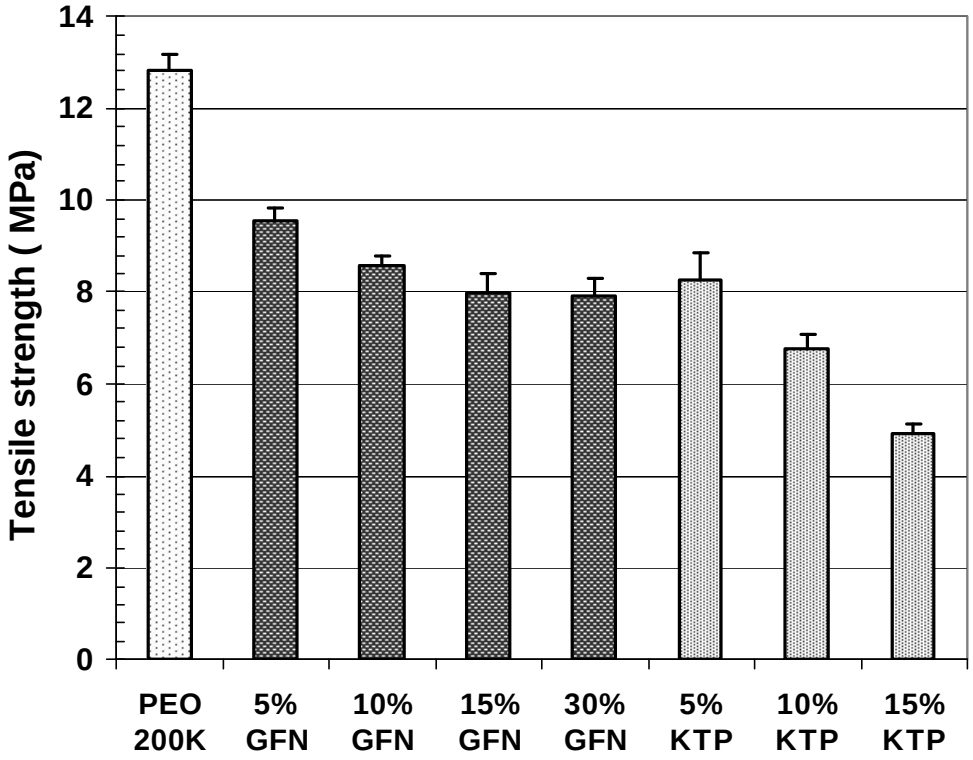

Figure 5.14: The tensile strength of hot-melt extruded polyethylene oxide (PEO) films and films containing various concentrations of guaifenesin (GFN) or ketoprofen (KTP), n=6.

In contrast to the guaifenesin containing films, the elongation of hot-melt extruded PEO films containing ketoprofen dramatically increased as the ketoprofen concentration increased. The percent elongation of the hot-melt extruded film containing 5% ketoprofen was 11% greater than the drug free PEO film. Furthermore, when the ketoprofen concentration in the film increased to 10% and 15%, the elongation increased 112% and 158% relative to the drug free PEO film, respectively. This represents more than a 2-fold increase in elongation when the ketoprofen concentration in the film was increased from 5 to 15%. Inclusion of ketoprofen in the film also reduced the tensile strength compared to the PEO film. Tensile strength decreased in an almost linear fashion as the ketoprofen content was increased from 5 to 15%.

Generally, the addition of a plasticizer increases the flexibility and ductility of a film and the elongation increases, but is accompanied by a reduction in film tensile strength and modulus of elasticity [14, 157, 172]. Plasticization therefore results in a soft, tough film. The mechanism by which plasticizers impart flexibility to a film is thought to be due to the presence of the plasticizer between polymer chains, which disrupts the forces holding the chains together and reduces the number of entanglements [66, 173, 174]. Increasing plasticizer concentration

enhances this effect. Thus, it can be concluded that ketoprofen was an excellent plasticizer when present at the 15% loading.

Solid particles have been found to reduce tensile strength, decrease elongation at break and increase film stiffness [175-178]. Crystallization of GFN in the film causes discontinuities in the polymeric network by disrupting hydrogen bonds between polymer segments. Although the GFN-PEO interaction probably occurs by a dipole-dipole interaction (since both are polar), this interaction is weaker than the broken hydrogen bonds between polymer chains. The polymer-GFN crystal interface constitutes a weak link in the film structure, creating stress. The stress caused by the crystals will increase as their concentration increases, reducing the tensile strength. GFN crystals also reduce the film elongation. Elongation has been considered a measure of the deformation capacity of a film. GFN crystals are flaws in the film which enhance the likelihood of rupture and failure, decreasing elongation.

The differences between the influence of GFN and KTP on the mechanical properties of the films can be attributed, in part, to their particle shape. Several researchers [179-181] have proposed that the stresses caused by solid particles in a polymeric network are generally dependent on the particle shape factor or aspect ratio. Guth defined the

shape factor as the ratio of length of the particle to its diameter [181]. Pigments with higher values of the shape factor have been found to increase the Young's modulus and the stress concentration in film coatings [176, 182-184]. The particle shape of guaifenesin and ketoprofen can be observed in the SEM micrographs in Figures 5.15 and 5.16. Internal stress is greater in the rod shaped GFN crystals compared with the plate-like KTP crystals.

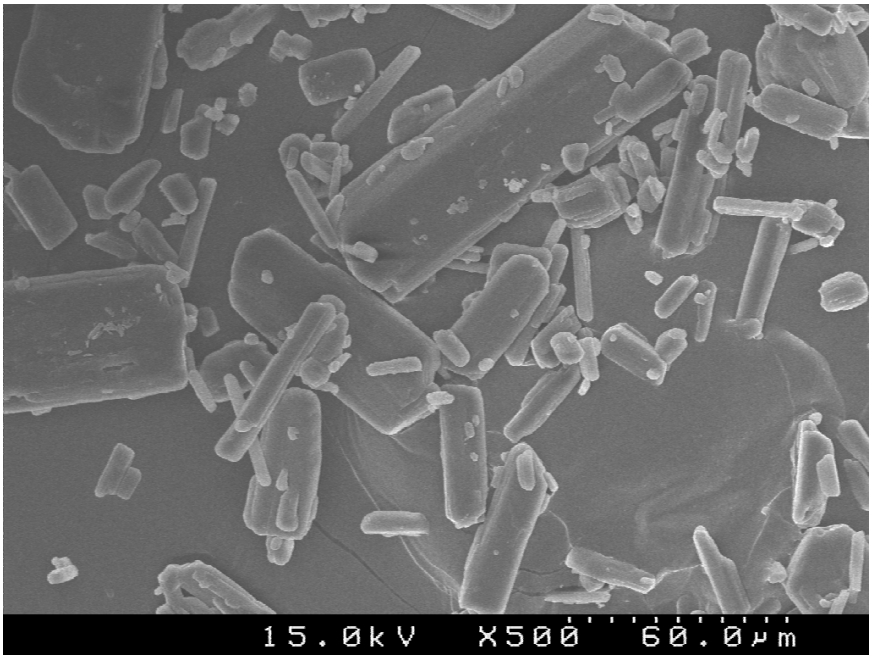

Figure 5.15: SEM micrograph of the surface morphology of guaifenesin at 500 x magnification.

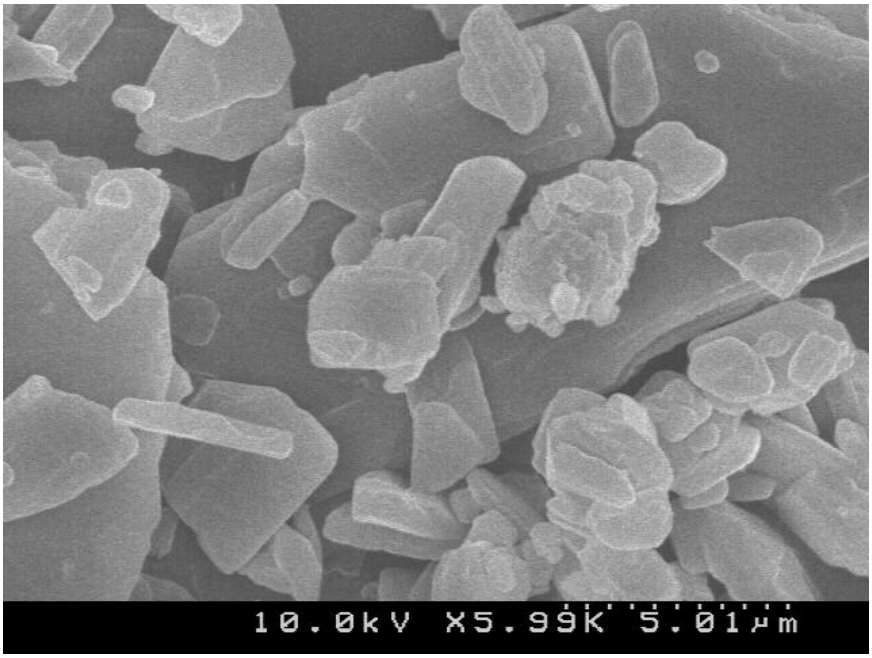

Figure 5.16: SEM micrograph of the surface morphology of ketoprofen at 5990 x magnification.

5.5 CONCLUSIONS

The results of this study demonstrate that guaifenesin and ketoprofen were stable during the extrusion process. XRD suggested that guaifenesin crystallized following the extrusion process, but ketoprofen formed a solid solution with PEO. Melting points corresponding to the crystalline drugs were not observed in the films by DSC analysis, suggesting that guaifenesin and ketoprofen dissolved in PEO while in the molten state. Crystallization of guaifenesin on the surface of the film could be observed using SEM at all concentrations studies, but did not reveal ketoprofen crystallization until reaching the 15% level. Guaifenesin and ketoprofen were found to decrease the drive load, increase the stability of PEO and plasticize the polymer during extrusion. The modified Hansen solubility parameter correctly predicted miscibility of PEO with ketoprofen and immiscibility between PEO and guifenesin. The percent elongation decreased with increasing guaifenesin concentrations, but significantly increased with increasing ketoprofen concentrations. Guaifenesin reduced the film elongation by disrupting the polymeric network. The elongation of films containing ketoprofen increased due to

plasticizing effects. Both guaifenesin and ketoprofen decreased the tensile strength of the film.

5.6 ACKNOWLEDGEMENTS

M. M. C. would like to thank the American Foundation for Pharmaceutical Education and the University of Texas at Austin Continuing Fellowship Program for their generous support.

CHAPTER 6 SUMMARY AND CONCLUSIONS

6.1 SUMMARY OF RESULTS

In this research project, hot-melt extrusion was successfully utilized to prepare pharmaceutical dosage forms. Three different systems were prepared: sustained release polyethylene oxide matrix that controlled the release rate of chlorpheniramine maleate by a diffusion and erosion mechanism; hydrophobic, diffusion controlled release ethyl cellulose tablets; and transdermal and transmucosal films which acted as a drug depot. The physicochemical and mechanical properties and mechanism of drug release of the extruded dosage forms were characterized using novel techniques. The influence of processing conditions, properties of the polymers, crystalline nature of the drug and polymer ad formulation variables were also investigated.

6.2 STABILITY OF POLYETHYLENE OXIDE IN MATRIX TABLETS PREPARED BY HOT-MELT EXTRUSION

The results of this study demonstrated that the thermal stability of PEO was dependent on both the storage temperature and the molecular weight of the polymer. Storage of the polymer above its melting point

significantly increased its degradation. Polymer degradation, when stored below its melting point, is due to oxygen permeation in the amorphous region of the polymer.

PEO matrix tablets prepared by hot-melt extrusion were sensitive to both process temperature and screw speed. The mechanism of polymer degradation during extrusion is both thermal and mechanical. At very high screw speeds, degradation is due to melt fracture. The amperage consumed by the extruder motor drive can be used as an indicator of polymer stability.

The addition of PEO 100K improved processing of PEO 1M and did not significantly influence the rate of CPM released from matrix tablets. Vitamin E, Vitamin E succinate and Vitamin E TPGS were found to be suitable stabilizers for PEO during processing. Vitamin E succinate and Vitamin E TPGS were dispersed at the molecular level in hot-melt extruded tablets. Ascorbic acid was shown to degrade the polymer in solution. Drug release rates from hot-melt extruded tablets stabilized with antioxidants were dependent on the hydrophilic nature of the antioxidant.

6.3 Physicochemical Properties and Mechanism of Drug Release from Ethyl Cellulose Matrix Tablets prepared by Direct Compression and Hot-melt Extrusion

The results of this study demonstrate that the guaifenesin release rate was dependent upon the particle size of ethyl cellulose and the processing conditions employed to prepare the tablets. The guaifenesin release rate was slower in tablets prepared with the “fine” ethyl cellulose particle size fraction due to the presence of fewer soluble drug clusters within the matrix. Tablets prepared by hot-melt extrusion exhibited considerably slower drug release relative to those prepared by direct compression. Thermal analysis demonstrated that guaifenesin was dispersed in ethyl cellulose at the molecular level in tablets prepared by hot-melt extrusion. The surface morphology of the hot-melt extruded tablets was found to depend upon processing temperature. The guaifenesin release rate also decreased with increasing compaction force in tablets prepared by direct compression due to greater densification of the powder bed. Analysis of the tablet pore characteristics could be correlated to the observed dissolution results. Drug release in hot-melt extruded tablets was found to be in good agreement with the Higuchi

Diffusion model. Tablets prepared by direct compression using "coarse" ethyl cellulose were found to release guaifenesin by both diffusion and erosion.

6.4 The Influence of Guaifenesin and Ketoprofen on the Properties of Hot-melt Extruded Polyethylene Oxide Films

The results of this study demonstrate that guaifenesin and ketoprofen were stable during the extrusion process. XRD suggested that guaifenesin crystallized following the extrusion process, but ketoprofen formed a solid solution with PEO. Melting points corresponding to the crystalline drugs were not observed in the films by DSC analysis, suggesting that guaifenesin and ketoprofen dissolved in PEO while in the molten state. Crystallization of guaifenesin on the surface of the film could be observed using SEM at all concentrations studies, but did not reveal ketoprofen crystallization until reaching the 15% level. Guaifenesin and ketoprofen were found to decrease the drive load, increase the stability of PEO and plasticize the polymer during extrusion. The modified Hansen solubility parameter correctly predicted miscibility of PEO with

ketoprofen and immiscibility between PEO and guifenesin. The percent elongation decreased with increasing guaifenesin concentrations, but significantly increased with increasing ketoprofen concentrations. Guaifenesin reduced the film elongation by disrupting the polymeric network. The elongation of films containing ketoprofen increased due to plasticizing effects. Both guaifenesin and ketoprofen decreased the tensile strength of the film.

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